STATE OF THE INDUSTRY

It's all about COVID-19

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Technology Q&A with Amwell’s Peter Antall, M.D.  Drugs in the Pipeline 2020 approvals
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Our annual State of the Industry reader survey is a peek into the window of what Managed Healthcare Executive® readers are thinking about and dealing with. We fully appreciate the limitations of such surveys. The way questions are framed can gloss over nuances. Answers may pigeonhole opinions and experiences that are more varied and layered. Reader surveys such as ours suffer from selection bias — they may tell us something about the people who took the time and trouble to fill out the survey, but the much larger pool of readers who didn’t fill it out are unaccounted for. This doesn’t mean that reader surveys aren’t worth doing. But as with everything else, it is a matter of recognizing their limitations and seeing them for what they are.

In a year with so many surprises, it was almost a relief that the responses to the State of the Industry had so few of them. We expected COVID-19 to reign supreme and it did. COVID-19 transmission, prevention and treatment far outdistanced the “chronic conditions” that ail American healthcare — high drug prices, consolidation of providers, underinsurance, under investment in prevention — when we asked respondents to rank healthcare issues. A sizable minority (41%) of our respondents are extremely concerned that a large percentage of Americans won’t get vaccinated against COVID-19, and about a third worry that the vaccine will be in short supply. One in 4 said the pandemic had severely reduced their organization’s revenues, although almost 1 in 5 said the pandemic had reduced their expenses — another example of how the COVID-19’s economic consequences seesaw, helping some (insurers have fared well, by and large) and hurting others (providers who depend on provision of in-person services).

As we went to press, two COVID-19 vaccines seemed likely to get FDA authorization. The COVID-19 pandemic has been a dark, tortuous chapter, but it’s one that large-scale vaccination could end, notwithstanding the legitimate concerns about many Americans not getting vaccinated.

Maybe next year’s State of the Industry survey will show a return to those good old-fashioned American healthcare concerns: high prices and cost, who is going to pay for it all and how that might happen.

Mike Hennessy Sr.
Chairman and Founder
of MJH Life Sciences™
A Comprehensive Approach to Long-Term Narcolepsy Management Is Important for Patients During Their Journey1-3

- Studies show that patients with narcolepsy are more likely to have certain comorbid medical conditions than those without narcolepsy4-6,a
- Narcolepsy is associated with substantial medical and economic burden, which may include emergency room visits, hospital visits, and/or absenteeism7,8,a

For more information, contact your Jazz Account Manager or visit NarcolepsyLink.com.

References:
Mission Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights and strategies to pursue value-driven solutions.
A Biden win, a Republican Senate and a slim Democratic majority in the House: That’s a recipe for compromise.

With the 2020 election season nearly behind us, conventional wisdom is that we will have divided government: a Democratic president, a Republican Senate and a razor-thin Democratic majority in the U.S. House of Representatives. That combination is a recipe for compromise on President-elect Joe Biden’s healthcare priorities; namely, the federal response to the COVID-19 pandemic and adjustments to the ACA.

The president-elect’s first priority is COVID, COVID, COVID. The COVID-19 task force that Biden created includes well-regarded former officials from the FDA and HHS. It seeks to promote national mask wearing and mandatory social distancing and to deploy a “textbook” public health approach to contact tracing and testing — a nationwide pandemic dashboard to display transmission rates of the virus in regions across the country. But Biden has stressed that lockdowns are not part of his plan.

As far as the ACA is concerned, the goal of the president-elect is to expand the law’s coverage provisions. Biden’s proposals would, by various means, expand coverage to include those who are out of work, those who are caught in the gap between Medicaid eligibility and qualifying for ACA subsidies, and those who have been systemically uninsured and uninsurable.

While there is potential for congressional compromise on Biden’s plans for COVID-19 and the ACA, the president-elect’s other policy proposals will meet swift and sure opposition in Congress, both from Republicans in the Senate and deficit hawks in the House. Legislation creating a “public option” will be difficult to pass, even though from the Democrats’ point of view the public option is a moderate plan and, politically, a way to deflect for the progressive wing of the party’s Medicare-for-all agenda. Biden’s proposal to tie ACA subsidies to the cost of more generous gold plans, as opposed to silver plans under the current law, also looks to be too big of a political lift. The policies could cost taxpayers upward of $750 billion and $200 billion over 10 years, respectively. Biden also proposed to lower the age of Medicare eligibility to 60 and to raise the income limits for ACA subsidy eligibility. They are also on the unlikely side of the political possibility spectrum.

The new administration figures to be aggressive about Medicaid expansion. Getting legislation passed is unlikely if the Republicans stay in control of the Senate. But Biden could use regulatory levers and financial incentives to move the dozen holdout states into the Medicaid expansion column. The president-elect has also indicated he’d take a hard line against approving new Medicaid work rules, which President Donald Trump’s administration deployed in numerous states for the first time in the program’s history. Formal requests from several states are still pending, and it’s unclear whether the Trump administration will finalize those waivers before departing in January. It’s also likely that incoming leadership at CMS will take a closer look at the work rules that have been approved and elect to rescind the regulations.

Drug pricing looks to be another area of contention. Biden has proposed allowing Medicare (and possibly Medicaid) to negotiate prices with drug manufacturers. House Democrats have passed and support such negotiations and reference pricing, which ties the price of physician-administered medications, and possibly other drugs, to prices paid in other countries.

Trump used executive orders to advance his health agenda with mixed rules. Biden’s goals are different, but the Democrat will also be using executive orders as a means to his ends. Biden’s orders may include demonstration authority to expand coverage and control costs, executive action to roll back restrictive policies in the Medicaid program and reinstatement of anti-discrimination protections for the LGBTQ community.

At the end of the day, these are best guesses based upon Biden campaign promises, conversations with people close to the campaign and transition, and historical beliefs of each party. The only thing we know for certain is that a new Congress will be installed on January 3, and Biden’s inauguration will take place on January 20.

Marc Samuels is CEO of ADVI, a strategic advisory services firm in Washington, D.C., that focuses on life sciences. He is a member of the Managed Healthcare Executive Editorial Advisory Board.
The polypill: Reducing risk — and maybe the unrealistic expectations

When Nicholas Wald and Malcolm Law proposed a pill in 2003 that would combine a statin with several blood pressure-lowering medications, they projected that such a “polypill” could lower the risk of stroke and heart attack risk by 80%.

But when polypills have been evaluated in clinical trials, the outcomes haven’t been nearly as impressive.

The results of a large international trial reported at the American Heart Association (AHA) Scientific Sessions 2020 meeting last month were no different. Compared with placebo, a daily polypill consisting of 40 milligrams of simvastatin, 100 milligrams of atenolol, 25 milligrams of hydrochlorothiazide and 10 milligrams of ramipril reduced serious cardiovascular events by 21%, according to an international team of researchers led by Salim Yusuf, D.Phil., executive director of the Population Health Research Institute in Hamilton, Ontario.

The addition of aspirin made a difference. In the group that took a 75-milligram dose of aspirin daily along with the polypill, the risk of a serious cardiovascular event was lowered by 31%. On the one hand, 80% versus 31% is a big difference. On the other hand, 31% is a big difference. The “on the other hand” is that a risk reduction of 31% is hardly minor. The authors and others heralded the results, which were published in the New England Journal of Medicine as well as presented at the AHA meeting, as an endorsement of the polypill.

Yusuf was quoted as saying that a global polypill-plus-aspirin strategy has the potential to prevent three million to five million cardiovascular deaths annually.

It’s hard to say whether a polypill will ever catch on in the U.S. and other wealthy countries. Drug manufacturers have an interest in keeping their medications siloed in those markets. In addition, some experts see the polypill as an one-size-fits-all approach in an era when, at least when it comes to treatment, the goal is increasingly to tailor the intervention to the individual.

Drug payments to physicians associated with increased prescribing

Drug companies paid U.S. physicians a total of about $2 billion in 2018 in the form of consulting and lecture fees, free meals and the like. A review of the research into those payments published in the Annals of Internal Medicine last month suggests that the drug companies may be getting a pretty good return on their investment.

Aaron P. Mitchell, M.D., M.P.H., an oncologist and health researcher at the Memorial Sloan Kettering Cancer Center in New York City, and his colleagues reported that 30 of 36 studies in their review found a positive association between drug company payments and increased prescribing of the paying drug company’s drugs. Moreover, there was a dose-response relationship in 25 of the studies: the greater the number of payments or the dollar amount of those payments, the greater the change in prescribing.

Mitchell and his co-researchers acknowledge that associations don’t prove cause and effect. Rather than inducing high prescribing, the payments from a drug company may go to physicians who are already high prescribers.
MA stargazing reveals a different story

All the Medicare Advantage trend lines seem like they are northward bound (see our story on page 10). Enrollment, the number of plans, the number of companies selling those plans — they’re all up. So Avalere Health’s report last month on the percentage of beneficiaries in highly rated plans stood out — and not in a good way.

CMS’ Star Rating program grades the quality of Medicare Advantage plans on a scale of 1 to 5 stars, with 5 being the highest quality.

Using data that the CMS made available in October, Avalere Health calculated that approximately 11.9% of the enrollees in Medicare Advantage plans that include drug coverage are in 5-star plans, which isn’t a big difference from the 11% of enrollees in 5-star plans last year. But the consulting firm’s numbers show that the proportion of enrollees in 4.5-star plans dropped sharply, from 31.4% last year to 19.6% this year, and the proportion in 4-star plans dipped from 38.8% last year to 30.9% this year.

Heart failure risk from diabetes moves into the limelight

The efficacy of SGLT2 inhibitors as a heart failure drugs is casting the cardiovascular risks of diabetes in a new light. For years, the focus has been on the atherosclerotic aspects of cardiovascular disease and retinopathy and other microvascular complications. Now heart failure is center stage.

Research results published in JAMA Cardiology last month add to the evidence that it belongs there. Using data from the National Health Interview Survey, Michael C. Honigberg, M.D., M.P.P., and his colleagues compared the incidence of hospitalizations for ischemic heart disease among adults who have diabetes with the incidence of hospitalizations for heart failure. From 1995 to 2015, both rates declined, but the incidence of hospitalizations from ischemic heart failure declined much faster — 67.8% compared with 38.9% for heart failure. By 2015 the incidence of hospitalizations for ischemic heart disease and heart failure among adults who have diabetes was essentially the same.

In Brief

Managed Healthcare Executive® has launched a second podcast, “MHE Talks: The Improving Patient Access Podcast.” Twice a month we’ll be talking to healthcare leaders about the multidimensional challenge of getting people the healthcare they need and deserve. The barriers can be financial, social, geographic, cultural — and often are a messy combination of these and many other factors.

In November, the podcast featured great conversations with John Henderson, president and CEO of the Texas Organization of Rural and Community Hospitals, and Leanne Berge, CEO of the Community Health Plan of Washington. You can find these and future episodes on our website at www.managedhealthcareexecutive.com/clinical/the-improving-patient-access-podcast.

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2020 drug approvals: not bad, considering

Pre-pandemic momentum helped keep the number of novel therapies approved by the FDA high, and then COVID-19 tested just how fast the pipeline could adjust and expand.

by JAIME ROSENBERG

Every nook and cranny of American healthcare has been affected by the COVID-19 pandemic, and drug development and approvals are no exception. But, remarkably, the number of drug approvals coming from the FDA showed no signs of slowing down this year, with 47 novel drugs approved as of the beginning of December, among them a record number of oncology drugs. Judging by Prescription Drug User Fee Act dates — dates by which the FDA is supposed to complete its review of an application — it looks like the number of FDA-approved new drugs this year will easily surpass the 48 approved last year but will probably fall short of the record of 59 approvals two years ago.

The COVID-19 effect

Does that mean that drug development escaped unscathed? No. As FDA drug approvals rolled in during the first half of the year, drug developers and those dependent on the pharmaceutical industry fretted that the number of approvals would fall off sharply as the year went on and the pandemic continued. In March, when the pandemic hit the United States, several drug companies moved to halt or delay new studies and patient enrollment.

But there was still some pre-pandemic momentum to the drug pipeline. If the pandemic has slowed down drug development and approvals, it will likely become more evident next year and the year after. Investigators are still trying to figure out safe, reliable ways to enroll and monitor patients in clinical trials, although steps have already been taken to do some trials remotely.

Looking at it from another perspective, the pandemic hasn’t crimped the drug pipeline so much as tested how fast it can expand and adjust as companies — with government assistance — raced to develop treatments and vaccines for a disease that didn’t exist before this year.

It hasn’t been all smooth sailing. According to many experts, the FDA emergency use authorizations (EUAs) for hydroxychloroquine, the drug touted by President Donald Trump, and convalescent plasma were a mistake — and in June the FDA did wind up revoking the EUA for chloroquine and hydroxychloroquine. The wisdom of full-fledged approval for Gilead’s Veklury (remdesivir) has also been questioned. On the other hand, as we went to press, the FDA was considering emergency use authorizations for two COVID-19 vaccines, one developed by Pfizer and BioNTech, a German company, and the other by Moderna, a biotech company in Cambridge, Massachusetts.

Specialty dominates

Meanwhile, in the “normal,” non-COVID-19 pipeline, there has been a marked shift recently in the types of drugs the FDA approves. The agency is approving more specialty drugs — expensive drugs for relatively rare diseases — than so-called traditional drugs. In fact, over the past five years, two-thirds of FDA approvals have been for specialty drugs, and 2020 is no exception, says Aimee Tharaldson, Pharm.D., senior clinical pharmacist of Emerging Therapeutics at Express Scripts. So far, 68% of 2020 approvals have been for specialty drugs. A large proportion of new drug approvals this year...
have been for oncology drugs. So far, 18 novel oncology drugs have gotten the nod from the FDA, and a few more may be approved before the year is over. According to Tharaldson, the oncology approvals this year break the record number of 17 approved in 2018.

Good time for orphans
The FDA is also approving orphan drugs at steady clip; Tharaldson notes that more than half of the new drugs approved so far in 2020 are in that category. Orphan drugs are a subset of specialty drugs that the FDA puts on a separate approval track that makes the developers eligible for a variety of incentives.

Two of the notable orphan drug approvals are for neuromyelitis optica spectrum disorder, a rare autoimmune disease that affects approximately 10,000 people in the United States. The disease, which can be misdiagnosed as multiple sclerosis, is characterized by inflammation of the optic nerve and spinal cord. Severe cases, can lead to blindness and impaired mobility. In June, the FDA approved Uplizna (inebilizumab-cdon), a CD19-directed antibody and, in August, Enspryng (satralizumab-mwge), an interleukin 6 inhibitor.

It is a different story with generics. According to Regulatory Focus, the online publication of the Regulatory Affairs Professionals Society, 2020 did not bode well for future generic competition. In fiscal year 2020, the FDA approved 909 abbreviated new drug applications (ANDAs) for generics, a 22% drop from fiscal year 2019, when the FDA approved 1,171 ANDAs.

Some notable 2020 FDA approvals of new drugs

Tepezza (teprotumumab-trbw). Approved in January, Tepezza is the first and only FDA-approved treatment for thyroid eye disease, a rare and progressive inflammatory disease that affects the eye and nearby orbital tissues that can result in eye protrusion and visual impairment.

Zeposia (ozanimod). Approved in March, Zeposia is a treatment for adults with relapsing forms of multiple sclerosis (MS), including relapsing-remitting MS, clinically isolated syndrome and active secondary progressive MS. Although it competes with Gilenya (fingolimod) and Mayzent (siponimod), the sphingosine-1-phosphate receptor modulator does not require first-dose monitoring for bradycardia (a slow heart rate).

Evrysdi (risdiplam). Approved in August, Evrysdi is the first oral drug approved to treat spinal muscular atrophy (SMA). The two other drugs approved for some patients with SMA are Spinraza (nusinersen), administered as an intrathecal injection once every four months, and Zolgensma (onasemnogene abeparvovec-xioi), a gene therapy administered as a one-time IV injection.

Some notable 2020 FDA approvals of new oncology drugs

Trodelvy (sacituzumab govitecan-hziy). Approved in April, Trodelvy is an antibody-drug conjugate for the treatment of patients with metastatic triple-negative breast cancer who received at least two prior therapies. The antibody “finds” the cancer, and the drug attacks the cancer.

Zepzelca (lurbinectedin). Approved in June, Zepzelca is an alkylating drug for adult patients with metastatic small cell lung cancer who have progressed on or after chemotherapy.

Sarclisa (isatuximab-irfc). Approved in March, Sarclisa is a monoclonal antibody that binds to the CD38 receptor on multiple myeloma cells. The FDA approval is for Sarclisa in combination with pomalidomide and dexamethasone for adult patients with multiple myeloma who have received at least two prior therapies.

Tabrecta (capmatinib). Approved in May, Tabrecta is a kinase inhibitor used to treat metastatic non-small cell lung cancer. It is one of an increasing number of agents that home in on cancer cells with a particular mutation, in this case a mutation that leads to MET exon 14 skipping.

Jaime Rosenberg is a freelance writer based in Jersey City, New Jersey.
Enrollment in Medicare Advantage (MA) plans has doubled over the past decade, and today the insurer-run plans cover more than 24 million Americans. Almost one-third of Medicare beneficiaries are now enrolled in MA plans, and that number is expected to grow as the baby boomers age into Medicare coverage.

Insurers see a large and growing line of business in MA. For beneficiaries, the simplicity of having coverage provided by a single plan is appealing. The premiums are low — and more than half of the MA plans in the United States have no monthly premium at all. Often additional coverage (dental, hearing) and other benefits (gym memberships) are also thrown in. The trade-off for the enrollees is a narrower network of providers and sometimes some copays and coinsurance.

The growth of MA is not without its critics. They see MA’s growing share of the Medicare population as a drift toward the privatization of Medicare — or at least the management of the program. Insurers are raking in large profits because of overly generous federal government payment, they say. The rebuttal from the MA plans and their backers MA brings the value, care coordination and focus on the social determinants of health (SDOH) that is sorely lacking elsewhere in American healthcare.

“This steady growth is likely due to the value and financial stability of these plans,” says Britta Orr, J.D., M.P.H., chief Medicare officer at Allina Health Aetna in suburban Minneapolis.

Over the years, MA plans have moved to address the physical, emotional and social needs of seniors and those eligible for Medicare because of disability, notes Susan Smith, senior vice president of the retail segment of Humana Medicare in Louisville, Kentucky. Smith mentions the gym membership, the MA perk that may be more common than important, and efforts to manage chronic health conditions. Additionally, a focus on SDOH has led to a greater emphasis on ensuring that members have enough healthy food to eat and access to programs that help them deal with loneliness and social isolation, Smith says.

MA plans may be especially attractive to people aging into Medicare who have had coverage through their employer and want to continue with the same insurer. Because Cigna has many members in its employer-sponsored plans, when these customers transition to Medicare, the insurer has the opportunity to offer continuity of care — and serve individuals throughout their lifetimes, says Aparna Abburi, president of Medicare Advantage at Cigna.

Tami Hibbitts, MBA, vice president of Medicare at Priority Health in Grand Rapids, Michigan, points to the appeal of MA coverage of preventive care, including annual health exams and a variety of screenings. Christopher Ciano, who oversees Aetna’s Medicare Advantage plans, mentions customization.

“By offering access to added benefits that can be tailored to support individual members’ unique lifestyles and total health needs, these (MA) plans are often referred to as a one-stop shop,” he says.

Financial incentives — and responsibilities

The MA plans say their preventive and SDOH efforts aren’t just selling points. “MA plan offerings and robust supplemental benefits lead to better health outcomes for members,” Hibbitts says.

“IT’s a win-win for everyone — the government, insurers and
members,” says Andrew Toy, president and chief technology officer at Clover Health in San Francisco. “Our goal is to keep our members happier, healthier and out of the hospital.” Clover partnered with Walmart this year to market MA plans in eight counties in Georgia that give members access to services at Walmart Health clinics with no copays.

Orr says taking on the financial risk of its MA members incentivizes Allina Health Aetna to keep coverage simple, personal and affordable. “The MA model challenges private insurers to provide high-quality networks, to promote population health and prevention, and to effectively coordinate patients’ care,” she says.

Still, the MA plans are dependent on government funds and Medicare, more specifically. “We take our stewardship of taxpayer dollars very seriously,” says Cigna’s Abburi says. “MA has traditionally been a pretty low-margin business.”

As with any government program, Orr says it’s important to strike the right balance between compensating Medicare plans sufficiently for the value they deliver and driving continuous improvement to quality and efficiency metrics.

Meanwhile, insurers continue to add new services to their MA plans to make them more attractive as the competition among MA plans heats up. According to the Kaiser Family Foundation, the average Medicare beneficiary had 33 MA plans to choose from during the enrollment period for 2021 coverage, which ended on Dec. 7.

Hibbitts says Priority Health believes that being healthy goes beyond visiting a doctor when you don’t feel well — it’s about practicing healthy habits every day. Next year the company’s MA plans are giving members free access to BrainHQ and its online brain exercises designed to improve memory and overall cognitive function.

Ciano describes several innovations in Aetna’s 2021 MA plans. For example, some are removing the requirement that beneficiaries designate a primary care physician. Instead, they can visit a nationally contracted walk-in clinic or CVS MinuteClinic location — CVS owns Aetna — and pay the same copay as a regular visit to a primary care provider.

All of Aetna’s 2021 MA plans will offer an annual in-home assessment at no cost that includes a comprehensive health risk assessment and noninvasive physical exam. The clinician will also assess the home environment for potential fall risks.

Aetna is also expanding its companionship benefit to address social isolation in select plans in six states. Aetna has hired a company called Papa Inc. to connect college-age young adults with older adults who need companionship and help with light housework and technology problems. Aetna also has a number of initiatives targeting the SDOH of food insecurity, including one that gives the members of some of its plans a “healthy food” debit card that gives the member a monthly allowance to purchase approved healthy food.

**Insurers in expansion mode**

Insurers don’t want to miss out on MA’s enrollment growth, so they are expanding into new markets. Cigna, for example, branched out and marketed 2021 MA plans in markets in five states — Ohio, Virginia, Oklahoma, Utah and New Mexico — for the first time while also expanding into new markets in states where it already has a presence.

When mapping out its expansion plans, Humana identifies areas where people with Medicare may be underserved with current offerings. “We’re already one of the largest MA organizations in the country based on membership, so there aren’t as many places for us to expand,” notes Smith. UnitedHealthcare has also gone into expansion mode, marketing 2021 MA plans in 291 additional counties. This is the company’s largest MA expansion in five years, according to Steve Warner, senior vice president of Medicare Advantage at UnitedHealthcare Medicare & Retirement.

Karen Appold is a medical writer in the Lehigh Valley region of Pennsylvania.
The usual approach to cancer treatment is to act fast and use some combination of surgery (if it is a solid, operable tumor), radiation and chemotherapy to get rid of as much of the cancer as possible.

But for many men with localized, low-grade prostate cancer, the best course seems to be active surveillance: closely monitoring the disease and putting off treatment until the cancer progresses. Active surveillance for prostate cancer is firmly in the mainstream of cancer treatment. The National Comprehensive Cancer Network (NCCN) and other groups have guidelines that say it is the preferred option for many men with localized, low-grade prostate cancer. Research reported last year in JAMA showed that the proportion of men with localized, low-grade prostate cancer who chose active surveillance or watchful waiting increased from 14.5% in 2010 to 42% in 2015. Watchful waiting is now commonly understood to mean monitoring the cancer but with no intention to treat it because of the patient’s age or poor health.

Active surveillance is commonly used to manage prostate cancer, because localized prostate cancer is often slow growing, is unlikely to metastasize and doesn’t cause symptoms. But physicians and patients take the same approach with some other similarly “indolent” cancers. The American Thyroid Association guidelines, for example, recommend active surveillance as an option for people with low-risk papillary thyroid cancer. Sometimes active surveillance is a strategy used after initial treatment — for example, it’s an option for men with early-stage testicular cancer who have had orchiectomy (surgery to remove one or both testicles).

As accepted as active surveillance has become, it still involves many gray areas and judgment calls. Is it an option for men whose prostate cancer is in the intermediate-risk category? The particulars of germline gene testing — which men should get it and which genes should be tested for — are still being hashed out. Research has shown that mutations in the BRCA1 and BRCA2 genes, plus a few others, are associated with aggressive, possibly lethal prostate cancer. The NCCN guidelines recommend germline testing for men with low- and intermediate-risk prostate cancer if they have a family history of inherited cancer or certain histologic findings. There is also the question of what exactly active surveillance should entail. Until fairly recently, men underwent invasive biopsies if rising PSA levels or abnormalities detected with a digital rectal exam suggested that their prostate cancer might be growing. Now it is an open question whether an MRI imaging, at least in some situations, might replace biopsies as a way of detecting the disease.

**Favorable results**

Regardless of the updates, active surveillance is fundamentally a wait-and-see approach to cancer. “It is a way of monitoring prostate cancer that isn’t causing any symptoms or problems,” says Ronald Tutrone Jr., M.D., FACS, of Chesapeake Urology in Baltimore.

Active surveillance of prostate cancer emerged as a strategy partly because widespread screening for the disease with PSA tests resulted in many more early cases being discovered. The U.S. Preventive Services Task Force recently recommended against this screening. But as men ages 55 to 69 continue to be screened, many have already been diagnosed with cancer and are now deciding how to handle their diagnosis.

Younger men with low-risk prostate cancer do not want to risk the urinary and sexual side effects of whole-gland treatments like surgery and radiation.” — Dan Sperling, M.D., DABR
Active surveillance: Men, clinicians are taking a wait-and-see approach to prostate cancer

Patients require treatment and that active surveillance can spare some men from the risk of treatment side effects, which include erectile dysfunction and urinary problems. But as Paryani notes, active surveillance is not without its risks. Repeat biopsies can also lead to erectile dysfunction and other problems. “Many patients opt not to pursue active surveillance due to this,” says Paryani, adding that the “anxiety of having a cancer diagnosis often plays a role as well.”

Advances in testing
Tutrone of Chesapeake Urology recently treated Baseball Hall of Famer Cal Ripken Jr., who received a diagnosis of prostate cancer earlier this year (Ripken was treated surgically and has told reporters the treatment was successful). Tutrone recommended a liquid biopsy test called the ExoDx Prostate Test. The developers of the urine-based test, which measures exosomal RNA associated with the presence of prostate cancer, say that it is a better indicator of prostate cancer risk than the conventional PSA test and therefore might help some men avoid unnecessary biopsies.

A study published in May 2020 showed that the ExoDx Prostate Test can influence clinician and patient behavior. Conducted in collaboration with CareFirst Blue Cross Blue Shield, a Blues plan in the Maryland; Washington, D.C.; and Northern Virginia market, this study included more than 1,000 patients and about 70 urologists. When the results of the ExoDx Prostate Test were used and evaluated in a clinical setting, 92% of patients followed the physician’s recommendation to defer having a prostate biopsy. “Payers really like it when patients follow physician recommendations,” Tutrone says. “And early detection of prostate cancer is key to saving lives and reducing costs over time.” The test was also associated with the discovery of more high-grade prostate cancers.

Rastinehad at Lenox Hill Hospital says that a “middle way” between active surveillance and treatment, called focal therapy, is being studied. Focal therapy zeroes in on small tumors in the prostate but leaves the rest of the gland intact. “In patients that are not great candidates for active surveillance but have disease we can see on MRI, we may be able to treat just the abnormal spot and keep men from having those unwanted side effects of surgery and radiation while still trying to achieve cancer control,” he says.

Keith Loria, a regular contributor to Managed Healthcare Executive®, is a freelance writer in the Washington, D.C., area.
Can you give an elevator-type-speech summary of Amwell? Who are your customers?

Our founders — our two CEO brothers (Ido and Roy Schoenberg) and a few others that they were working with way back in 2006 — had a vision to create a platform that allows patients and providers to interact electronically. That was a different time back then — it was before we even had such a thing as the smartphone. It was really based on the technology at that time, which was computers.

But once we moved into a whole new phase of technology available to consumers with smartphones and tablets, the vision just expanded from there. I think that vision still holds true. We really are about creating technology — primarily software but also hardware — and creating essentially an ecosystem that allows healthcare to be delivered in a robust way in an electronic way.

To date, a lot of the telehealth that’s happened has been done by creating a cadre of providers who are exclusively available by telehealth and hence not providers known to the patients. Little by little over time, providers in the community have embraced telehealth. COVID supersized that. So now really what we’re seeing is that providers en masse have embraced telehealth. Patients have embraced telehealth.

So does that mean that Amwell is increasingly working with physician groups and setting them up to provide telehealth services to their existing panel of patients? It does. We certainly work directly with providers and with large provider groups and hospital systems.

We also work with health plans. They often are the ones that bring the demand — they have many, many members. Importantly, what health plans can also bring is telehealth as a reimbursable event. And we work with tech companies as well. Telehealth is broadening and expanding into new areas like remote patient monitoring. We worked with Apple on the Apple Heart Study looking at the use of a smartwatch to detect a heart condition. You may have seen our recent investment from Google.

Could you compare and contrast Amwell to Teladoc?

We are often compared in the marketplace. Our names come up in unison, regularly. I have some colleagues and friends over there, and I respect the work that they do. But we are fundamentally different companies and with different strategies.

I think Teladoc has done extremely well and executed well in the employer space and in the health plan space. They’ve worked hard to execute in the health system space, but I would argue that they have been behind us in that space for many years. What’s really different about us, though, is that we are about the software and the hardware, and when we provide software to an organization, we white label it under their brand.

So the average patient, who might have taken advantage of a telehealth service provided by their doctor or a specialist in a hospital system, they wouldn’t know necessarily that they were experiencing an Amwell experience.

That’s correct. I mean, it sounds hokey to say, but to borrow from another company and another technology, we are sort of the Intel inside. We provide a plug-and-play software solution or hardware solution.

Is there any sort of salient statistic that illustrates Amwell’s growth in 2020?

In quarter 2 of this year, our volumes were up 300% over quarter 1. Our monthly active providers in quarter 2 were up 400% over those in quarter 1 across all of
our platforms. In April of 2020, the average daily visits on our platforms went to over 40,000 visits per day. And that’s compared to 5,500 in January of this year. And if we look all the way back a year earlier, to April of 2019, we had 2,900 visits a day, on average. So, dramatic increases.

That sort of growth can be hard to cope with. So what sort of bottlenecks or friction points have there been at Amwell?

In the second quarter it was an all-hands-on-deck moment, as it was for most healthcare providers around the country.

When you are a software company, you plan for 2x, 3x, 4x growth. You don’t plan for such dramatic growth overnight. There was some scrambling there to the hosting requirements. There was a shift to a little bit more cloud-based hosting and some other things that I’m probably not qualified to comment on.

On the patient-care side, we needed a lot more providers very quickly. And we needed to bring them on in a way in which they were properly trained and qualified and credentialed. We did see some surges in in wait times very briefly. And we got those quickly under control, as we brought on more and more providers.

As we look forward, the challenges are not acute like that. The challenges are more around regulations, around reimbursement — some of the traditional barriers that have inhibited providers from engaging. During COVID, there have been a lot of waivers of regulations and waivers of certain restrictions on reimbursement. Our goal now is to make permanent those waivers that make sense — not all of the waivers will. We expect the waiver of enforcement of HIPAA to go back.

So let’s just discuss HIPAA waiver. My understanding is that the HIPAA waiver allowed physicians to use platforms that weren’t specific to telehealth to communicate with patients.

I think the way I would describe it is that they allowed providers to use technologies that are not traditionally HIPAA compliant, as long as they’re being used in a good faith effort to provide care during the public health emergency.

**So why do you think that waiver should end?**

HIPAA is there to protect patients and their personal health information. Some people sometimes quibble with some of the challenges in maintaining HIPAA compliance, but I think we’re all aligned on that. We don’t want our personal health information sitting on servers at Apple, for example, which they very well may be right now if you’ve used FaceTime for a medical visit. You know, there are certain protections like HIPAA that that are in place for, I believe, good reasons.

I think that we all recognize, and I think we heard loud and clear from providers who were newly engaging in telehealth during the COVID pandemic that ease of use is now a priority. You can have ease of use and HIPAA compliance. We have developed another version of our platform — we call it Amwell Now — to satisfy both of those needs. It’s HIPAA compliant, just like all of our technology is, but it’s built to be simple and easy to use, not full of bells and whistles, not all about interoperability and multiple levels of complexity.

**Not to be argumentative, but ending the HIPAA waiver would benefit companies like Amwell because you have a medical-grade, HIPAA-compliant product.**

I don’t see it that way. During the COVID pandemic, many more companies entered the telehealth space. Our traditional competition may have been Teladoc. Now our competition may very well be Microsoft Teams, Zoom and all these other folks. They’re well within their rights, and they have plenty of coders to make sure that their products are also HIPAA compliant.

I think that the way we see it is that regulations exist for certain reasons. I see HIPAA as simply protecting people’s privacy. ▶

This transcript has been edited for clarity and length.
The pandemic opens a window of opportunity

The decrease in in-person healthcare this year because of the COVID-19 pandemic could be a good thing for telehealth and programs that deliver hospital-level care at home. by SUSAN LADIKA

According to research reported in Morbidity and Mortality Weekly Report, by the end of June, about 40% of American adults had delayed or avoided medical care, and a sizable proportion — 12% — had put off urgent or emergency care. Those most likely to avoid urgent care had underlying health conditions, were Black or Hispanic, were young, had disabilities, or served as unpaid caregivers.

As the number of COVID-19 cases and deaths decreased in many parts of the country during the summer months, the provision of medical services bounced back to a certain extent. It is too soon to tell what impact the escalating number of cases and deaths in November will have. Although the economic indicators this year are a mixed bag, the economic disruptions caused by the pandemic have factored into many people’s decision to skip medical care, observes Trzcinski: “Many can’t afford an unexpected medical bill.” And millions of people have lost their jobs, along with their health insurance, as a result of the pandemic. “People are making hard decisions — paying for health insurance or paying for rent,” she says.

Can telehealth step in? Of course, the decline in in-person care has been accompanied by the much-talked-about surge in telehealth, especially for behavioral health problems. The Forrester researchers estimate that American consumers will make roughly 480 million telehealth visits this year, with almost 40% of those visits for behavioral health care. The research firm predicts a slight drop next year to about 440 million visits. But the evidence of the shift to telehealth is overwhelming. Research results reported in JAMA Network Open in October showed that in 2018 and 2019, between 122 million and 130 million primary care visits occurred each quarter and that only 1% of those visits were conducted virtually. During the second quarter of this year, the number of primary care visits dipped to fewer than 100 million, but 35% of those visits were conducted virtually. “It’s anybody’s guess how long the pandemic will significantly pressure patients and clinicians to use telemedicine in settings where
they might otherwise engage face-to-face,” says lead author G. Caleb Alexander, M.D., M.S., a professor of epidemiology and medicine at the Johns Hopkins Bloomberg School of Public Health. Alexander believes that telehealth can be used successfully when patients have an ongoing relationship with a primary care provider. He has qualms, though, about depending on a telehealth visit when a clinician is seeing a patient for the first time or dealing with a new complaint. It can be “very hard to evaluate them properly using telemedicine,” says Alexander.

During a recent webinar on 2021 healthcare predictions, Sam Glick, an Oliver Wyman partner and leader of the consulting firm’s innovation center, said telehealth usage represented 70% to 80% of care during the height of the pandemic and is expected to account for 30% to 50% of care going forward. Primary care physicians are using telehealth to improve the continuity of care, Glick observed, but he said the change was in its infancy. Glick’s prediction: Virtual visits that are not integrated into someone’s healthcare record, such as care provided through Teladoc or a similar service, “will be commoditized and compete with urgent care.”

**Primary care underutilized**

Andrew J. P. Carroll, M.D., FAAFP, a family physician in Chandler, Arizona, and member of the board of directors of the American Academy of Family Physicians, says his office pivoted to virtual care “really out of necessity” and as a way to maintain continuity care for patients with chronic conditions and for those with COVID-19. Carroll says that in some cases, patients who have skipped routine care during the pandemic ended up having to receive costly emergency care.

Even before the pandemic began, consumers were forgoing visits to primary care physicians, according to Forrester’s research. A study published in the *Annals of Internal Medicine* in February found that from 2008 to 2016, visits to primary care physicians dropped by about 25% for adults under the age of 65, and the proportion of adults making no visits to their primary care provider in a year jumped from 38% to 46%.

“I don’t think telemedicine is going to solve our historic problem of underutilization of primary care,” says Alexander. And as primary care visits fell, visits to urgent care clinics, retail clinics and emergency departments climbed 47%. Trzcinski at Forrester says that healthcare clinics at retail locations such as Walmart and CVS have benefited because of their price transparency and convenience.

The primary care visit isn’t the only type of care that has declined since the pandemic began. A drop in hospital usage is projected to cost health systems $350 billion this year, according to Forrester. According to the research firm’s predictions report, emergency department visits have fallen by 42%, outpatient visits by 35%, and in-patient care by 22%.

Hospitals have responded, in part, by providing hospital-level care to patients in their homes. Results of what appears to be the first randomized controlled trial looking at the effectiveness of hospital-at-home care were reported last year in the *Annals of Internal Medicine*. Lead author David M. Levine, M.D., M.P.H., M.A., of Brigham and Women’s Hospital in Boston, and his colleagues found that the average cost of an acute care episode was almost 40% lower for patients receiving hospital-at-home care compared with those who were traditional inpatients. The hospital-at-home patients had fewer lab tests, imaging studies and consultations. They were less sedentary, and their 30-day readmission rate was 7% compared with 23% for those receiving care in the hospital.

Levine says that hospital-at-home care is common in many industrialized countries: “We are pretty far behind.” Levine is doing his part to change that and expects to have two more studies published in the next month or so. One challenge has been the number of patients who declined to receive care at home. “We’ve spent 100 years telling people the best care is at the hospital,” Levine says. “We need to prove they can get high-quality, safe care at home.” Another one has been reimbursement, says Levine. “There is no easy payment mechanism,” he notes. “That’s one of the reasons why it hasn’t taken off in the U.S.”

Susan Ladika is a health and business writer in Tampa, Florida.
In 2016, SPINRAZA became the first FDA-approved treatment for SMA and is approved in 50+ countries worldwide.1,2

3-80
DAYS
11,000+
YEARS
3,700+

Has treated SMA in patients 3 days* to 80 years1,4,11
11,000+ patients treated with SMA worldwide45
3700+ adults with SMA treated worldwide45

FDA=US Food and Drug Administration; SMA=spinal muscular atrophy.
*Includes clinical trial patients.
†Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Clinical studies of SPINRAZA included patients from 3 days to 16 years of age at first dose.
‡Based on commercial patients in the US (including Puerto Rico) through June 2020.
§Based on commercial patients, early access patients, and clinical trial participants through June 2020.

INDICATION
SPINRAZA® (nusinersen) is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.
In 2016, SPINRAZA became the first FDA-approved treatment after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications, including acute severe thrombocytopenia, have been observed.

† Based on commercial patients in the US (including Puerto Rico) through June 2020.

Coagulation abnormalities and thrombocytopenia

SPINRAZA® (nusinersen) is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

*Includes clinical trial patients.

IMPORTANT SAFETY INFORMATION (continued)

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed. Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months. Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

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

SPINRAZA® (nusinersen) injection, for intrathecal use
Brief Summary of Full Prescribing Information

1 INDICATIONS AND USAGE
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION
2.1 Dosing Information
SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage
The recommended dosage is 12 mg (5 mL) per administration.

Initiate SPINRAZA treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose
If a loading dose is delayed or missed, administer SPINRAZA as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

2.2 Important Preparation and Administration Instructions
SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation
• Store SPINRAZA in the carton in a refrigerator until time of use.
• Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use external heat sources.
• Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored. The use of external filters is not required.
• Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
• Administer SPINRAZA within 4 hours of removal from vial.

Administration
• Consider sedation as indicated by the clinical condition of the patient.
• Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
• Prior to administration, remove 5 mL of cerebrospinal fluid.
• Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation [see Adverse Reactions (6.3)].

2.3 Laboratory Testing and Monitoring to Assess Safety
Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:
• Platelet count
• Prothrombin time; activated partial thromboplastin time
• Quantitative spot urine protein testing

3 DOSAGE FORMS AND STRENGTHS
Injection: 12 mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia and Coagulation Abnormalities
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

5.2 Renal Toxicity
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.
SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of SPINRAZA-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS
The following serious adverse reactions are described in detail in other sections of the labeling:
- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

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

In clinical studies, 346 patients (47% male, 76% Caucasian) were treated with SPINRAZA, including 314 exposed for at least 6 months, 258 exposed for at least 1 year, and 138 exposed for at least 2 years. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days to 16 years of age at first dose) with symptomatic SMA; in a sham-controlled trial in infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=84 for SPINRAZA, n=42 for control); an open-label study in presymptomatic infants (Study 3, n=25) and other studies in symptomatic infants (n=54) and later-onset patients (n=103). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)
In Study 1, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in Study 1 were infants, adverse reactions that are verbally reported could not be assessed in this study.

Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Infantile-Onset SMA (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg¹ N=80 %</th>
<th>Sham-Procedure Control N=41 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory infection²</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Loading doses followed by 12 mg (5 mL) once every 4 months
² Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenzal, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis.
In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

**Clinical Trial in Later-Onset SMA (Study 2)**

In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain.

**Table 2. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Later-Onset SMA (Study 2)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg&lt;sup&gt;1&lt;/sup&gt; N=84 %</th>
<th>Sham-Procedure Control N=42 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>1</sup> Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

**6.2 Immunogenicity**

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

The immunogenic response to nusinersen was determined in 294 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Seventeen patients (6%) developed treatment-emergent ADAs, of which 5 were transient, 12 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, “persistent” is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.
6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested (see Data). 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. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0.6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.

8.2 Lactation

Risk Summary

There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established [see Clinical Studies (14.1)].

Juvenile Animal Toxicity Data

In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1 or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use

Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities

Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs [see Warnings and Precautions (5.1)].

Renal Toxicity

Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity [see Warnings and Precautions (5.2)].

Manufactured for:

Biogen
Cambridge, MA 02142

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It’s all about COVID-19

We conducted our annual State of the Industry reader survey in October and November and had close to 100 respondents. Thanks to everyone who participated! Not all of items could be included here, so check out our website for the full results.
Respondents ranked the importance of healthcare issues on a scale of 1-8. Here we show the proportion of first, second and third rankings each issue received.

Please rate your level of agreement with the following statements.

- **Americans overutilize healthcare.**
  - Agree: 53%
  - Neutral: 23%
  - Disagree: 24%

- **Drug prices are high, but high prices mean investment in research and development.**
  - Agree: 29%
  - Neutral: 9%
  - Disagree: 62%

- **High-deductible health plans have been effective in slowing down the growth in healthcare spending.**
  - Agree: 28%
  - Neutral: 18%
  - Disagree: 54%

- **American healthcare would benefit from some form of Medicare for all.**
  - Agree: 41%
  - Neutral: 9%
  - Disagree: 50%

- **CMS should negotiate drug prices.**
  - Agree: 73%
  - Neutral: 11%
  - Disagree: 16%

- **The increasing enrollment in Medicare Advantage is a positive development.**
  - Agree: 56%
  - Neutral: 23%
  - Disagree: 19%

- **The ACA has, by and large, been a positive development in American healthcare.**
  - Agree: 52%
  - Neutral: 23%
  - Disagree: 25%

- **Value-based care arrangements can reduce healthcare spending but not by a lot.**
  - Agree: 49%
  - Neutral: 25%
  - Disagree: 26%
What is your general feeling about the current state of American healthcare?

What is your level of concern regarding these COVID-19 vaccine issues?

- The vaccine(s) will be in short supply: 32% Extremely concerned, 11% Not concerned
- The vaccine(s) will reflect and worsen healthcare disparities among racial and ethnic groups: 35% Extremely concerned, 15% Not concerned
- The vaccine(s) will be unsafe: 21% Extremely concerned, 10% Not concerned
- Multiple vaccines will create confusion: 22% Extremely concerned, 19% Not concerned
- The vaccine developers will profit at public expense: 28% Extremely concerned, 23% Not concerned
- A large percentage of Americans won’t get vaccinated: 41% Extremely concerned, 10% Not concerned

Note: Responses of “concerned” and “mildly concerned” were removed.

Rate the Trump administration’s response to the COVID-19 pandemic.

- Poor: 6%
- Fair: 20%
- Neutral: 5%
- Good: 22%
- Excellent: 47%

Continued on page 28
Updates in treatment of adult spinal muscular atrophy

**Spinal muscular atrophy (SMA)** is a motor neuron disease that begins at birth and is caused by a mutation in SMN, the survival motor neuron gene. Patients gradually lose motor function abilities, including the ability to walk. The arms and legs are generally affected, although patients may also experience difficulties with breathing and swallowing.

In this K-Cast video series, experts in the management of SMA provide an overview of the disease, including types of SMA, how patients typically present, common symptoms and how clinicians assess motor function.

The experts also discuss nusinersen, the first medication to treat the underlying cause of SMA. Nusinersen is an antisense oligonucleotide that helps increase the amount of functional SMN protein. In addition, the discussants talk about clinical trial data demonstrating the efficacy and safety profile of nusinersen in adults, as well as their real-world experiences in treating patients with nusinersen. This article includes highlights from three episodes of this K-Cast video series.

**EPISODE 1**

**Overview of spinal muscular atrophy**

*Wymer:* SMA is a genetic, gradually progressive motor neuron disease that is present in about 1 in every 11,000 births. Patients with SMA experience a gradual loss of motor function. The primary cause is a mutation in SMN, the survival motor neuron gene, typically a deletion of SMN1. A second copy, SMN2, has reduced SMN protein function compared with SMN1. There are different types of SMA, depending on how much SMN2 there is to cover for the loss of SMN1. Patients with SMA can present in different ways, but they all show the same pattern of gradually progressive muscle weakness.

**EPISODE 4**

**Nusinersen in adults with 5Q SMA**

*Wymer:* An observational study analyzed 14 months of data from 124 patients aged 16 to 55 years. The results showed that a high percentage of patients either stabilized or showed some modest improvement [with nusinersen]. It may not have cured their disease, but it prevented their decline.

*Hagenacker:* We tested the drug [nusinersen] in adults, and we found that it is also efficacious and safe in this population. In every case, we found a significant improvement of motor function. Treatment should be initiated as early as possible for the best effects on motor function. Also, patients cannot be too old to get on treatment.

**EPISODE 5**

**Real-world experience treating SMA with nusinersen**

*Wymer:* We treat the patient [with nusinersen] and we find stabilization of their disease. There may be modest improvements. I don't see dramatic improvement. But what I don't see is patients continuing to decline. [Based on] my own personal experience, it's been well-tolerated and patients have done well.

*Hagenacker:* My experience with nusinersen in the treatment of adult patients is that it is typically well-tolerated. It's an efficacious drug. Patients improve or even stabilize, and we haven't ever seen this before, so it is an important drug in the treatment of adult SMA.

**Tim Hagenacker, M.D.**  
University Hospital Essen  
Essen, Germany

Dr. Hagenacker’s research interests include pathomechanisms of neuropathic pain, neurotoxicity and neuroprotective strategies in the peripheral nervous system.

**James Wymer, M.D., FAAN**  
University of Florida Health  
Gainesville, Florida

Dr. Wymer is a neurologist and professor who specializes in the diagnosis and management of neuromuscular diseases, muscle diseases and peripheral neuropathies.
Respondents ranked the performance of Trump healthcare officials as poor, fair, neutral, good or excellent. Alex Azar’s rankings had the highest proportion of “poor”; Anthony Fauci’s, the highest proportion of “excellent.”

By what proportion has the COVID-19 pandemic increased your organization’s use of, payment for, or involvement in telehealth and other forms of virtual care?

How has the COVID-19 pandemic affected the revenues of your organization?

- Severely reduced them: 26%
- Moderately reduced them: 45%
- No effect: 18%
- Moderately increased them: 10%
- Greatly increased them: 1%

How has the COVID-19 pandemic affected the expenses of your organization?

- Severely increased them: 46%
- Moderately increased them: 20%
- No effect: 17%
- Moderately reduced them: 16%
- Greatly reduced them: 2%
What proportion of your value-based arrangements involves downside risk?

- 0-25%
- 66%
- 26-50%
- 29%
- 51-75%
- 2%
- 76-100%
- 3%

Rate the effect that the COVID-19 pandemic has had on your organization's adoption of, payment for, or involvement in value-based care this year and next.

- No effect
- Negative effect
- Moderate increase
- Slight increase
- Great increase
- 9%
- 46%
- 23%
- 16%
- 5%

Where would you place your organization in the shift toward value-based care?

- Have not yet started
- 18%
- Have a few cost-only initiatives started
- 21%
- Is focused mostly on value-care
- 52%
- Have a few quality-only initiatives
- 10%
- Have many cost/quality initiatives
- 39%
- 32%

What proportion of your value-based arrangements involves downside risk?

- Accountable care organization
- 52%
- Bundled payment/episodes of care
- 39%
- Pay for performance
- 56%
- Other
- 19%
At AllianceRx Walgreens Prime, our innovative approach to specialty pharmacy puts your members at the center of everything we do. Our extensive clinical expertise, data-driven insights and robust suite of programs help you:

- Reduce cost of care
- Improve member outcomes
- Simplify member experience

We partner closely with you to develop customized solutions that help you achieve success. Learn how we can help at www.alliancerxwp.com.
How much of your organization's executive/management compensation is value driven (meaning you receive it only if your organization reaches certain value-based metrics for quality or cost)?

- 1% - 5%: 49%
- 6% - 10%: 15%
- 11% - 15%: 9%
- 16% - 20%: 9%
- More than 21%: 18%

Has your organization taken meaningful steps this year to address health disparities and racism?

- Yes: 72%
- No: 28%

What proportion of the executives in your organization are Black or Latino?

- 0% - 9%: 46%
- 10% - 19%: 28%
- 20% - 29%: 13%
- 30% - 39%: 8%
- 40% - 49%: 1%
- 50% or greater: 3%

Rate your confidence that the focus on, and discussion of, health disparities and racism this year will result in meaningful change.

- Very low: 14%
- Low: 21%
- Neutral: 49%
- High: 15%
- Very high: 2%
How specialty pharmacies lower healthcare costs

Specialty pharmacies can prevent costly incidents and improve adherence through specialized patient-support services, making them uniquely positioned to help payers and pharmacy benefit managers (PBMs) meet the crucial need in healthcare of lowering costs.

Read our white paper where we explore how specialty pharmacies maximize patients’ health so their overall healthcare spend is lower:
BiologicsSP.com/payers
Drug treatment is entering a dazzling new era of increasingly precise, bespoke medications that work in ways that were the stuff of science fiction just a few years ago: T cells modified to home in on cancer cells, antibody-drug conjugates that recognize only disease-causing cells, therapies that hinder a disease process at the molecular level by snipping DNA or stifling gene expression so the process can go no further.

The rub: their high cost

In her keynote address, Alex Jung described some reasons specialty medications are so costly but also offered hope and insight into how those costs will eventually come down. Jung, partner and managing director at EY-Parthenon, a consulting subsidiary of Ernst & Young LLP, also said that examples from the medical benefit side of healthcare payment show how payment for high-cost medications might be better managed.

Costs and prices will decrease, she said, through higher utilization and repetition.

"Repetition helps us uncover patterns and approaches that can be standardized or shifted to lower-cost resources," said Jung, whose talk was sponsored by Managed Healthcare Executive.

Jung also discussed the many factors that ratchet up the cost through the value chain. Hospitals may need to renovate their facilities to accommodate sterile lab requirements and patient infusion rooms. The drug development process needs to be tightly controlled to "zero defect" standards, partly because the medications are so sensitive and made up of human cells. Conditions need to be more precisely and accurately diagnosed, often at the genetic level, and patients often need to be more closely monitored after they receive a treatment.

"When you are putting modified genes into a human being, you have to monitor the person very carefully to ensure that you haven't done something to alter gene expression in another part of the body," said Jung, adding that this monitoring may wind up affecting labor costs.

Regardless of the cost issues, because of the promise of a potential cure, Jung said that she expected high demand for these therapies from affected patients and that providers and payers will have to adapt.

Providers, she said, "can't just write a prescription for a bunch of pills in a bottle going forward, because patients are going to demand something a little bit more potent if they know there is a potential cure for them, especially if they have a high mortality or morbidity profile. They are going to have an opportunity to seek cures."

Jung told the forum audience that industry needed to shift to a focus on improving processes rather than

"I would love PBMs to have a culture of innovation when it comes to therapy and the solutions they bring to market around patient therapies."

Alex Jung

Continued on page 34
After more than 40 years of tackling the toughest medical challenges, we know that approaching any problem from a single point of view is setting a course for failure.

Success depends upon welcoming diverse approaches, challenging the status quo and exploring hypotheses from all angles. Science demands diversity and so do we.

TO LEARN MORE ABOUT OUR COMMITMENT TO DIVERSITY AND INCLUSION, VISIT GENE.COM
The tools of prescription drug utilization management — step therapy and prior authorization — can help guarantee that the right patients get the right treatments while also controlling costs. But these methods are being exploited beyond their original intent, and some patients suffer needlessly, according to panelists in this session at the 4th Annual Pharmacy Benefit Management Institute® (PBMI) Specialty Pharmacy Rx Forum.

Sharon (Frazee) Phares, Ph.D., M.P.H., senior vice president for research and data innovation, Pharmaceutical Strategies Group (PSG); Renee Rayburg, RPh, vice president of specialty clinical consulting for Artemetrx at PSG; and Ted Okon, MBA, executive director of the Community Oncology Alliance (COA), joined Jonathan Ogurchak, Pharm.D., CSP, CEO and co-founder of STACK, for a discussion centered on a recent white paper from Phares and Rayburg titled “Should All Drugs Be Treated Equally When It Comes to Utilization Management?”

The white paper, which was supported by Genentech, argued that utilization management can be helpful when used appropriately. But when applied to the complex cases seen in specialty pharmacy, the results feel more like a war of attrition, with patients and their doctors worn down by delays or denials.

Both the paper and the discussion focused on prior authorization for multiple sclerosis (MS) and rheumatoid arthritis treatments and in oncology, where delays in getting necessary drugs can result in disease progression — or worse.

Okon and COA have been outspoken about a policy change that has allowed step therapy in Medicare Advantage, which he calls “fail first.” In recent years, discussions at COA’s annual meeting have escalated when angry oncologists described patients developing brain metastases while they waited for an insurer to approve a therapy.

In their white paper, Phares and Rayburg described a “time equals brain,” referring to evidence that delays in treatment for patients with MS could result in more significant disability, including accelerated loss of brain volume.

The panelists described cases of patients being forced to take drugs they knew wouldn’t work and then having to pay another copay when the drug they needed in the first place was approved. Employers...
Indications:
SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:
• Treatment-resistant depression (TRD) in adults.
• Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:
• The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.1
• SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.1

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.1

MDD=major depressive disorder.

Important Safety Information (continued)

**Cognitive Impairment**

Short-Term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO® caused cognitive performance decline 40 minutes post-dose. SPRAVATO®-treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO® and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment: Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO® nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO® have not been evaluated beyond one year.

**Impaired Ability to Drive and Operate Machinery**: Before SPRAVATO® administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO®.

**Ulcerative or Interstitial Cystitis**: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO® nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO®-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO® and refer to an appropriate healthcare provider as clinically warranted.

**Embryo-fetal Toxicity**: SPRAVATO® may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO® in utero. Advise women of reproductive potential to consider pregnancy planning and prevention.

**DRUG INTERACTIONS**

**CNS depressants (e.g., benzodiazepines, opioids, alcohol)**: Concomitant use may increase sedation. Closely monitor for sedation with concomitant use of CNS depressants.

**Psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil)**: Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of psychostimulants.

**Monoamine oxidase inhibitors (MAOIs)**: Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of MAOIs.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**: SPRAVATO® is not recommended during pregnancy. SPRAVATO® may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO® in utero. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO®, treatment with SPRAVATO® should be discontinued and the patient should be counseled about the potential risk to the fetus.

**Pregnancy Exposure Registry**: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/

**Lactation**: SPRAVATO® is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO®.

**Females and Males of Reproductive Potential**: SPRAVATO® may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO®.

**Pediatric Use**: The safety and effectiveness of SPRAVATO® in pediatric patients have not been established.

**Geriatric Use**: Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO®, 12% were 65 years of age and older, and 2% were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age. The mean esketamine Cmax and AUC values were higher in elderly patients compared with younger adult patients.

The efficacy of SPRAVATO® for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO® plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥65 years of age. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

**Hepatic Impairment**: SPRAVATO®-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO® has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

**DRUG ABUSE AND DEPENDENCE**

**Controlled Substance**: SPRAVATO® contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act. Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional, non-therapeutic use of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO® may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment, and to be “spaced out.” Monitoring for signs of abuse and misuse is recommended.

**ADVERSE REACTIONS**

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypotension, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypotension, vomiting, euphoric mood, and vertigo.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, on previous pages.
Important Safety Information (continued)

CONTRAINDICATIONS
SPRAVATO® is contraindicated in patients with:
• Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
• History of intracerebral hemorrhage.
• Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS
Sedation: In clinical trials, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% of SPRAVATO®-treated patients experienced loss of consciousness. Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. Closely monitor for sedation with concomitant use of SPRAVATO® with CNS depressants (see Drug Interaction (7.1)).
SPRAVATO® is available only through a restricted program under a REMS.
Dissociation: The most common psychological effects of SPRAVATO® were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of SPRAVATO®-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO®; treatment should be initiated only if the benefit outweighs the risk. Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.
SPRAVATO® is available only through a restricted program under a REMS.
Abuse and Misuse: SPRAVATO® contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient’s risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.
SPRAVATO® is available only through a restricted program under a REMS.
SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO® is available only through a restricted program called the SPRAVATO® REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. Important requirements of the SPRAVATO® REMS include the following:
• Healthcare settings must be certified in the program and ensure that SPRAVATO® is:
  • Only dispensed and administered in healthcare settings.
  • Patients treated in outpatient settings (e.g., medical offices and clinics) must be enrolled in the program.
  • Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO®.
• Pharmacies must be certified in the REMS and must only dispense SPRAVATO® to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies, is available at www.SPRAVATOREMS.com or 1-855-382-6022.

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 adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO® is not approved in pediatric (<18 years of age) 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. Monitor all antidepressant-treated patients 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 SPRAVATO® and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.
Increase in Blood Pressure: SPRAVATO® causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours. Approximately 8% to 19% of SPRAVATO®-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO® is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing SPRAVATO®, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risk. Assess BP prior to administration of SPRAVATO®. In patients whose BP is elevated prior to SPRAVATO® administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO® therapy should take into account the balance of benefit and risk in individual patients.
BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficits) immediately for emergency care.
Closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants or monoamine oxidase inhibitors (MAOIs) (see Drug Interactions (7.2, 7.3)).
In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, on previous pages.
**SPRAVATO® (esketamine) nasal spray, CIII**

Brief Summary

BEFORE PRESCRIBING SPRAVATO®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

**WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS**

Sedation

- Patients are at risk for sedation after administration of SPRAVATO [see Warnings and Precautions].

Dissociation

- Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO [see Warnings and Precautions].

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see Warnings and Precautions].

Abuse and Misuse

- SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse [see Warnings and Precautions].

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS [see Warnings and Precautions].

**Suicidal Thoughts and Behaviors**

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric, adolescent, and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients [see Warnings and Precautions].

**INDICATIONS AND USAGE**

SPRAVATO® is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

**Limitations of Use:**

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated [see Clinical Studies (14.2) in Full Prescribing Information]. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.

- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

**CONTRAINDICATIONS**

SPRAVATO is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation [see Warnings and Precautions]

- History of severe aseptic or hemorrhagic [see Warnings and Precautions]

- Hypersensitivity to esketamine, ketamine, or any of the excipients.

**WARNINGS AND PRECAUTIONS**

**Sedation**

In clinical trials, 48% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) [see Adverse Reactions], and 0.3% to 0.4% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/S score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see Dosage and Administration (2.4) in Full Prescribing Information].

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants [see Drug Interactions].

**Dissociation**

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including distortion of time, space and illusions), depersonalization and derealization (61% to 84% of SPRAVATO-treated patients experienced one or more of these disorderly changes). SPRAVATO patients developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale [see Adverse Reactions].

Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

**SPRAVATO® (esketamine) nasal spray, CIII**

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see Dosage and Administration (2.4) in Full Prescribing Information].

SPRAVATO is available only through a restricted program under a REMS [see Warnings and Precautions].

**Abuse and Misuse**

SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient’s risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence [see Drug Abuse and Dependence].

SPRAVATO is available only through a restricted program under a REMS [see Warnings and Precautions].

**SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)**

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse [see Boxed Warning and Warnings and Precautions].

Important requirements of the SPRAVATO REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO is:
  - Only dispensed and administered in healthcare settings.
  - Patients treated in outpatient settings (e.g. medical offices and clinics) must be enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO [see Dosage and Administration (2.4) in Full Prescribing Information].

- Pharmacies must be certified in the REMS and must only dispense SPRAVATO to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies is available at www.SPRAVATOrems.com or 1-855-382-6022.

**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 (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in 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. Most drug studies studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (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 with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients**

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>18-24</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>5 additional patients</td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer patient</td>
</tr>
<tr>
<td>&gt;65</td>
<td>6 fewer patients</td>
</tr>
</tbody>
</table>

* SPRAVATO is not approved 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 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...
SPRAVATO® (esketamine) nasal spray, CIII

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 SPRAVATO and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure
SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 4 hours (see Adverse Reactions). Approximately 8% to 19% of SPRAVATO-treated patients and 1% to 4% of placebo-treated patients experienced an increase of greater than or equal to 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage) (see Contraindications). Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks. Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO administration (as a general guide: >140/90 mmHg) a decision to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO administration [see Dosage and Administration (2.1, 2.4) in Full Prescribing Information]. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOis) (see Drug Interactions).

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment
Short-Term Cognitive Impairment
In a randomized, double-blind study of healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort required for cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery
Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive (see Clinical Studies (14.3) in Full Prescribing Information). The effects of SPRAVATO 84 mg were comparable to placebo at 6 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of the studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO.

Ulcereative or Interstitial Cystitis
Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients (see Adverse Reactions). No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year. Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.
### Table 2: Adverse Reactions Occurring in ≥2% of Adult TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD (continued)

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>SPRAVATO + Oral AD (N=346)</th>
<th>Placebo + Oral AD (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness*</td>
<td>101 (29%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Sedation*</td>
<td>79 (23%)</td>
<td>21 (9%)</td>
</tr>
<tr>
<td>Headache*</td>
<td>70 (20%)</td>
<td>38 (17%)</td>
</tr>
<tr>
<td>Dysgeusia*</td>
<td>66 (19%)</td>
<td>30 (14%)</td>
</tr>
<tr>
<td>Hypoesthesia*</td>
<td>63 (18%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Lethargy*</td>
<td>37 (11%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Dysarthria*</td>
<td>15 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>12 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>11 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

### Psychiatric disorders

| Dissociation* | 142 (41%) | 21 (9%) |
| Anxiety*      | 45 (13%)  | 14 (6%) |
| Insomnia      | 29 (8%)   | 16 (7%) |
| Euphoric mood | 15 (4%)   | 2 (1%)  |

### Renal and urinary disorders

| Pollakiuria     | 11 (3%)  | 1 (0.5%) |

### Respiratory, thoracic and mediastinal disorders

| Nasal discomfort* | 23 (7%)  | 11 (5%)  |
| Throat irritation  | 23 (7%)  | 9 (4%)   |
| Oropharyngeal pain| 9 (3%)   | 5 (2%)   |

### Skin and subcutaneous tissue disorders

| Hyperhidrosis    | 14 (4%)  | 5 (2%)   |

* The following terms were combined:

- **Anxiety includes:** agitation; anticipatory anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panic attack; tension
- **Blood pressure increased includes:** blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
- **Dissociation includes:** delusional perception; depersonalization/derealization disorder; derealization; delusion; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; oculomotor disorder; oral dysesthesia; pain; perception altered; tinnitus; vision blurred; visual impairment
- **Dizziness includes:** dizziness; dizziness exertional; dizziness postural; procedural dizziness
- **Dysarthria includes:** dysarthria; slow speech; speech disorder
- **Dysgeusia includes:** dysgeusia; hypogeusia
- **Headache includes:** headache; sinus headache
- **Hypothalamic response:** hypothalamic; hypothalamic, hypothalamic oral, hypothalamic hypothalamic
- **Lethargy includes:** fatigue; lethargy
- **Nasal discomfort includes:** nasal crusting; nasal discomfort; nasal dryness; nasal pruritus
- **Sedation includes:** altered state of consciousness; hypersonmia; sedation; somnolence
- **Tachycardia includes:** extrasystoles; heart rate increased; tachycardia
- **Vertigo includes:** vertigo; vertigo positional

### Table 3: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD and Acute Suicidal Ideation or Behavior Treated with SPRAVATO + Oral AD and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>SPRAVATO + Oral AD (N=227)</th>
<th>Placebo + Oral AD (N=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia*</td>
<td>8 (4%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

### Ear and labyrinth disorders

| Vertigo | 14 (6%) | 1 (0.4%) |

### Gastrointestinal disorders

| Nausea | 26 (11%) | 12 (5%) |
| Vomiting | 22 (10%) | 14 (6%) |
| Constipation | 8 (4%) | 6 (3%) |
| Dry mouth | 5 (2%) | 2 (1%) |

### General disorders and administration site conditions

| Feeling drunk | 8 (4%) | 1 (0.4%) |
| Feeling of relaxation | 5 (2%) | 3 (1%) |

### Investigations

| Blood pressure increased* | 34 (15%) | 14 (6%) |

### Musculoskeletal and connective tissue disorders

| Myalgia | 5 (2%) | 1 (0.4%) |

### Nervous system disorders

| Dizziness* | 103 (45%) | 34 (15%) |
| Sedation*  | 86 (36%)  | 27 (12%) |
| Dysgeusia* | 46 (20%)  | 29 (13%) |
| Hypoesthesia* | 30 (13%) | 4 (2%) |
| Lethargy*  | 10 (4%)   | 4 (2%)  |
| Confusional state | 5 (2%) | 0 (0%) |

### Psychiatric disorders

| Dissociation* | 108 (48%) | 30 (13%) |
| Anxiety*      | 34 (15%)  | 20 (9%)  |
| Euphoric mood | 17 (7%)   | 1 (0.4%) |
| Intentional self-injury | 7 (3%) | 3 (1%) |
| Dysphoria     | 5 (2%)    | 0 (0%)   |

### Renal and urinary disorders

| Pollakiuria* | 5 (2%) | 2 (1%) |

### Respiratory, thoracic and mediastinal disorders

| Oropharyngeal pain | 10 (4%) | 3 (1%) |
| Throat irritation | 9 (4%) | 5 (2%) |

### Skin and subcutaneous tissue disorders

| Hyperhidrosis* | 11 (5%) | 5 (2%) |

* The following terms were combined:

- **Anxiety includes:** agitation; anxiety disorder; fear; irritability; nervousness; panic attack; psychomotor hyperactivity; tension
- **Blood pressure increased includes:** blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
- **Dissociation includes:** delusional perception; depersonalization/derealization disorder; derealization; delusion; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; oculomotor disorder; oral dysesthesia; pain; perception altered; tinnitus; vision blurred; visual impairment
- **Dizziness includes:** dizziness; dizziness exertional; dizziness postural; procedural dizziness
- **Dysarthria includes:** dysarthria; slow speech; speech disorder
- **Dysgeusia includes:** dysgeusia; hypogeusia
- **Headache includes:** headache; sinus headache
- **Hypothalamic response:** hypothalamic; hypothalamic, hypothalamic oral, hypothalamic hypothalamic
- **Lethargy includes:** fatigue; lethargy
- **Nasal discomfort includes:** nasal crusting; nasal discomfort; nasal dryness; nasal pruritus
- **Sedation includes:** altered state of consciousness; hypersonmia; sedation; somnolence
- **Tachycardia includes:** extrasystoles; heart rate increased; tachycardia
- **Vertigo includes:** vertigo; vertigo positional
- **Hyperhidrosis includes:** cold sweat; hyperhidrosis
- **Hypothalamic response:** hypothalamic; hypothalamic, hypothalamic oral, intranasal hypothalamic; pharyngeal hypothalamic
- **Lethargy includes:** fatigue; lethargy; psychomotor retardation
- **Pollakiuria includes:** micturition urgency; pollakiuria
- **Sedation includes:** sedation; somnolence; stupor
- **Tachycardia includes:** heart rate increased; sinus tachycardia; tachycardia
SPRAVATO® (esketamine) nasal spray, CIII

Sedation

Sedation was evaluated by adverse event reports and the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S). In the MOAA/S, 5 means “responds readily to name spoken in normal tone” and 0 means “no response after painful trapezius squeeze.” Any decrease in MOAA/S from pre-dose is considered to indicate the presence of sedation, and such a decrease occurred in a higher number of patients on SPRAVATO than placebo during the short-term TRD studies. Dose-related increases in the incidence of sedation (MOAA/S score <5) were observed in a fixed-dose TRD study [see Warnings and Precautions]. Table 4 presents the incidence of sedation (MOAA/S score <5) in a fixed-dose study with adult patients ≥65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, there was a higher incidence of sedation (MOAA/S score <5) in patients treated with SPRAVATO plus oral AD compared to patients treated with placebo plus oral AD, similar to the TRD study results described above.

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥25 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results in Table 6.

Table 4: Incidence of Sedation (MOAA/S Score <5) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients ≥65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

<table>
<thead>
<tr>
<th></th>
<th>Patients ≤65 years</th>
<th>Patients ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>N=112</td>
<td>N=116</td>
</tr>
<tr>
<td>MOAA/S Score &lt;5</td>
<td>11%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>61%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>

*Patients who were evaluated with MOAA/S

Dissociation/Perceptual Changes

SPRAVATO can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing and resolution was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADSS). A CADSS total score of more than 4 indicates the presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on SPRAVATO compared to placebo during the short-term TRD studies. Dose-related increases in the incidence of dissociative symptoms (CADSS total score >4 and change >0) were observed in a fixed-dose TRD study [see Warnings and Precautions]. Table 5 presents the incidence of dissociation (CADSS total score >4 and change >0) in a fixed-dose study with adult patients ≥65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥25 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results described above.

Table 5: Incidence of Dissociation (CADSS Total Score >4 and Change >0) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients ≥65 Years of Age with TRD and Flexible-Dose Study with Patients ≥65 Years of Age with TRD)

<table>
<thead>
<tr>
<th></th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure ≤110 mmHg</td>
<td>9 (3%)</td>
<td>13 (4%)</td>
<td>13 (4%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Diastolic blood pressure ≤25 mmHg</td>
<td>11 (4%)</td>
<td>37 (32%)</td>
<td>37 (32%)</td>
<td>37 (32%)</td>
</tr>
</tbody>
</table>

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥25 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results described above.

Table 6: Increases in Blood Pressure in Double-blind, Randomized, Placebo-Controlled, Short-Term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD in Adult Patients

Table 7: Incidence and Severity of Nausea and Vomiting in a Double-blind, Randomized, Placebo-Controlled, Fixed-Dose Study in Adult Patients with TRD

<table>
<thead>
<tr>
<th>Treatment (+ Oral AD)</th>
<th>N</th>
<th>All</th>
<th>Severe</th>
<th>N</th>
<th>All</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRAVATO 56 mg</td>
<td>115</td>
<td>31(27%)</td>
<td>0</td>
<td>7(6%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SPRAVATO 84 mg</td>
<td>116</td>
<td>37(32%)</td>
<td>4(3%)</td>
<td>14(12%)</td>
<td>3(3%)</td>
<td></td>
</tr>
<tr>
<td>Placebo Nasal Spray</td>
<td>113</td>
<td>12(11%)</td>
<td>0</td>
<td>2(2%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral antidepressants demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patient with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥25 mmHg increases in SBP, and similar rates of increases to DBP ≥110 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results described above.

Drug Interactions

Central Nervous System Depressants

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation [see Warnings and Precautions]. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Psycho stimulants

Concomitant use with psycho stimulants (e.g., amphetamines, methylphenidate, methamphetamine, dextroamphetamine) may increase blood pressure [see Warnings and Precautions]. Closely monitor blood pressure with concomitant use of SPRAVATO with psycho stimulants.

Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure [see Warnings and Precautions]. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

Use in Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.
Risk Summary
SPRAVATO® is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of esketamine and ketamine, SPRAVATO may cause fetal harm when administered to pregnant women (see Data). Advise pregnant women of the potential risk to an infant exposed to SPRAVATO in utero. There are risks to the mother associated with untreated depression in pregnancy (see Clinical Considerations). If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

SPRAVATO® contains esketamine hydrochloride, the (S)-enantiomer of ketamine, and is a Schedule III controlled substance under the Controlled Substances Act.

Postnatal Day (PND) 9, and the effect normalized by PND 19 in treatment groups as compared with PND 14 for the majority of the control animals. There is no NOAEL for this delay in sensory/motor response observed in pups during the preweaning period. During the postweaning period, a decrease in motor activity was observed at doses ≥ 15 mg/kg which is 0.5-times the human exposure at the MRHD of 84 mg/day. The NOAEL for maternal toxicity and decreased motor activity during the postweaning period was 4.5 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-times the AUC exposure at MRHD of 84 mg/day.

Lactation
Risk Summary
Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfeeding infant or on milk production. Published studies in juvenile animals report neurotoxicity (see Data). Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

Pediatric Use
The safety and effectiveness of SPRAVATO in pediatric patients have not been established. Clinical studies of SPRAVATO in pediatric patients have not been conducted.

Geriatric Use
The efficacy of SPRAVATO for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥ 65 years of age. SPRAVATO was initiated at 14 mg twice weekly and could be titrated to 56 mg or 84 mg administered twice-weekly. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment
The mean esketamine AUC and τ1/2 values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function [see Clinical Pharmacology (12.3) in Full Prescribing Information]. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Drug Abuse and Dependence
Controlled Substance
SPRAVATO contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.
Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol. SPRAVATO may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be “spaced out”. Monitoring for signs of abuse and misuse is recommended.

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a Schedule III controlled substance and has known abuse potential. In this study, the mean “Drug Liking at the Moment” and “Take Drug Again” scores for single doses of intranasal SPRAVATO (84 mg and 112 mg – the maximum recommended dose and 1.3 times the maximum recommended dose, respectively) were similar to these scores in the intravenous ketamine (0.5 mg/kg infused over 40 minutes) control group. However, these scores were greater in the SPRAVATO and ketamine groups compared to the placebo group. The 112 mg dose of intranasal SPRAVATO was associated with significantly higher scores for “Hallucinating,” “Floating,” “Detached,” and “Spaced Out” than the 84 mg dose of intranasal SPRAVATO and the intravenous ketamine dose.

Dependence

Physical dependence has been reported with prolonged use of ketamine. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dosage reduction of a drug. There were no withdrawal symptoms captured up to 4 weeks after cessation of esketamine treatment. Withdrawal symptoms have been reported after the discontinuation of frequently used (more than weekly) large doses of ketamine for long periods of time. Such withdrawal symptoms are likely to occur if esketamine were similarly abused. Reported symptoms of withdrawal associated with daily intake of large doses of ketamine include craving, fatigue, poor appetite, and anxiety. Therefore, monitor SPRAVATO-treated patients for symptoms and signs of physical dependence upon the discontinuation of the drug.

Tolerance has been reported with prolonged use of ketamine. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Similar tolerance would be expected with prolonged use of esketamine.

OVERDOSE

Management of Overdose

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Contact a Certified Poison Control Center for the most up to date information on the management of overdose (1-800-222-1222 or www.poison.org).

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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Multiple sclerosis needs a “higher touch” approach

Patients may need help obtaining medication for MS, which is a complicated business, said William Trombatt and James Adams of AllianceRx Walgreens Prime. By Deborah Abrams Kaplan

Just over 900,000 people in the U.S. live with multiple sclerosis (MS), according to a study funded by the National Multiple Sclerosis Society, and by some estimates, the average lifetime medical cost is $4.1 million. Getting patients into treatment quickly and keeping them on treatment are crucial not only to decrease the chances of the disease worsening but also to keep costs and healthcare utilization down.

“Patients should stay on their therapy indefinitely, as long as their condition hasn’t changed,” said William Trombatt, Pharm.D., CSP, manager of clinical programs for specialty and home delivery pharmacy for AllianceRx Walgreens Prime, at the Pharmacy Benefit Management Institute’s Specialty Rx Forum. Those adhering to MS treatments are 42% less likely to relapse and require 52% fewer hospitalizations, as well as having fewer outpatient visits.

The need for a “higher touch” program is important for patients with MS, said Trombatt’s colleague and co-presenter at the meeting, James Adams, chief information officer for AllianceRx Walgreens Prime. People with MS can’t just walk into a regular pharmacy to quickly fill a prescription like many people with other condition can do, he noted. “There’s a tremendous amount of coordination between the pharmacy, doctor and insurance company before the patient...
Putting the patient at the center of specialty pharmacy

Paula Bickley, vice president of market access for Biologics by McKesson, discussed how to make patient-centeredness more than just a tagline.

By Keith Loria

Specialty pharmacy plays an important role in the overall healthcare ecosystem, providing a patient-centric approach to coordinating numerous aspects of patient care and disease management.

According to the Academy of Managed Care Pharmacy, those involved in specialty pharmacy look to efficiently deliver medications that often require special handling, storage and distribution requirements. Specialty pharmacies are also designed to improve clinical and economic outcomes for patients with complex, often chronic, and rare conditions through close contact and management by clinicians.

But don’t lose sight of the patient, Paula Bickley, vice president of market access for Biologics by McKesson, reminded attendees of the Pharmacy Benefit Management Institute’s Specialty Rx Forum.

During a session titled “Putting the Patient First,” Bickley said the phrase shouldn’t be just a marketing tagline. Providers must build care platforms that engage patients and capture significant opportunities to improve clinical and economic outcomes for patients with complex, often chronic, and rare conditions through close contact and management by clinicians.

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“Patient-centeredness also means working with patients so they can afford medications, Bickley noted. “We have experts who all they do all day is complete financial assessment for patients, really trying to understand what their true affordability or financial concerns are.” The experts help patients secure nonprofit copay grants or manufacturer reimbursement copay cards, she said. Bickley mentioned a CMS study that showed that at a cost threshold of about $500 roughly 1 in 4 patients with a cancer diagnosis didn’t initiate treatment because of the cost.

Keith Loria is a freelance writer in the Washington, D.C., area.