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FDA Extends Xeljanz Safety Warnings to Other JAK Inhibitors

The FDA is requiring revisions about increased risk of serious heart-related events such as heart attack, stroke, cancer, blood clots and death to the labels of the Janus kinase (JAK) inhibitors indicated for inflammatory conditions: Pfizer Inc.'s Xeljanz/Xeljanz XR (tofacitinib), Eli Lilly and Co.'s Olumiant (baricitinib) and AbbVie Inc.'s Rinvoq (upadacitinib). The move follows the agency's review of a large, randomized safety clinical trial of Xeljanz. The FDA also is limiting the approved uses for all the drugs to certain people who have not responded to or cannot tolerate at least one tumor necrosis factor (TNF) inhibitor. While some payers may already have had TNF inhibitors as a first step, they need to make sure that they have utilization management strategies in place to help ensure these drugs are used in the second-line setting, recommend industry experts.

The trial compared Xeljanz with TNFs in people with rheumatoid arthritis (RA) and showed an increased risk of blood clots and death with a lower dose of Xeljanz. A prior study whose results Pfizer disclosed on Jan. 27, 2021, showed the same results but at a higher dose.

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FDA Approves Byooviz, First Ophthalmology Biosimilar in U.S.

The FDA approval of the first biosimilar for ocular use is poised to bring savings to a costly class, particularly in Medicare. However, ophthalmologists' and retinologists' lack of experience with biosimilars is a potential roadblock to these drugs' uptake. Payers should focus on provider education and outreach ahead of these drugs' launches in order to ease concerns about their use, say industry experts.

On Sept. 20, the FDA approved Samsung Bioepis Co., Ltd. and Biogen Inc.'s Byooviz (ranibizumab-nuna) for the treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV) (see brief, p. 8). The drug is a biosimilar of Roche Group unit Genentech USA, Inc.'s Lucentis (ranibizumab). Under an agreement with Genentech, Samsung Bioepis and Biogen will be able to market the therapy in the U.S. in June 2022.

According to Magellan Health, Inc. division Magellan Rx Management's eleventh annual Medical Pharmacy Trend Report, released in May, ophthalmic injections accounted for the second-highest category of spend in Medicare in 2019, behind only oncology. Lucentis ranked No. 5 in the top 10 Medicare medical benefit drugs by spend. Among commercial plans, Lucentis had 20% of the ophthalmic injectable market, behind Genentech's Avastin (bevacizumab), with 32%, and Regeneron Pharmaceuticals, Inc.'s Eylea (aflibercept), with 37%. In Medicare, Lucentis had a 22% share, compared with 43% for Avastin and 27% for Eylea, and in Med-

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icaid, Lucentis had an 18% share of the market, compared with Avastin's 55% and Eylea's 27%.

Those drugs, along with Novartis Pharmaceuticals Corp.'s Beovu (brolucizumab-dbll), are vascular endothelial growth factor (VEGF) inhibitors that are injected directly into a person's eye.

"Eylea dominates the branded products in market share, and Lucentis is the second most highly utilized FDA-approved ophthalmic VEGF inhibitor," Dea Belazi, Pharm.D., M.P.H., president and CEO of AscellaHealth, tells AIS Health, a division of MMIT. "Avastin, used off-label for ophthalmic indications, represents the third most highly utilized VEGF inhibitor most likely due to its very low cost (about $200 per year)."

Beovu, notes Winston Wong, Pharm.D., president of the W-Squared Group, has showed "a higher rate of vision loss and blindness due to occlusive retinal vasculitis, retinal artery occlusion and intraocular inflammation" that "has pretty much taken it out of the market. The FDA updated the label to reflect these safety concerns."

Avastin's $200 annual price compares with $8,000 per year for Beovu, $12,025 for Eylea and $25,350 for Lucentis, says Rachel K. Anderson, Pharm.D., C.S.P., clinical program manager at AllianceRx Walgreens Prime. If Byooviz is priced at a 20% discount to Lucentis, that would put its price at $20,280.

"The impact and uptake of Byooviz will be directly related to the cost at which this biosimilar enters the market," maintains Renee Rayburg, R.Ph., vice president of specialty clinical consulting at Pharmaceutical Strategies Group, who adds that biosimilars generally come onto the U.S. market at a discount of 10% to 30% off the reference product's price.

The anti-VEGF space "is an interesting category where there is no clear superior agent," says Wong. "I believe what drives the debates of 'which agent to use' is cost from the payer perspectives. Retinal specialists, while they do look at cost, are also considering clinical efficacy, familiarity with the anti-VEGF product and manufacturer loyalty." Avastin is being used off-label, he explains, "which technically goes against most medical policies, especially in the early years, and there have been reports of adverse reactions associated with the compounding of bevacizumab. There is also current biosimilar bevacizumab on the market" although professional societies are speaking out against those agents' use in ocular settings (see story, p. 6). "It is my understanding that approximately 50% of practices administer bevacizumab as a first-line agent; however, it is not known if they are being cost conscious or if this is being mandated by the payer through step therapy."

'Biosimilar Market Entry Is Welcome'

"Given limited treatment options in this space and lack of competition, biosimilar market entry is welcome and bound to be impactful with regard to options to choose from and cost," maintains Robert Kinyua, Pharm.D., senior director of clinical program development at Prime Therapeutics LLC.

"Many of the ophthalmic conditions, if left untreated, can lead to vision impairment or blindness," says Samsung Bioepis spokesperson Anna Nayun Kim. "It is important that patients receive treatment at the right time, but many patients are still undertreated, often due to financial reasons. The introduction of a safe and effective biosimilar for Lucentis may play a role in reducing the economic burden placed on patients and health care systems by current neovascular age-related macular degeneration (nAMD) therapies and expand patients' access to this treatment option and support the

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implementation of an effective treatment regimen."

According to Anderson, Byooviz's approval "marked a monumental milestone in the biosimilar landscape.… This is significant because it opens the door for competition in the market as well as expands patient access to critical medication. With an aging population and growing need to treat chronic, complex conditions, specialty biologics are on the rise. In an environment where health decisions are increasingly made on cost, biosimilars like Byooviz will play an important role in improving access to these types of medicines. The launch of biosimilars over the next decade could save consumers a significant amount of money; further, increased affordability may boost access to treatments for millions of patients who may otherwise have forgone treatment or compromised for less effective treatment."

Byooviz is Samsung Bioepis' fifth FDA-approved biosimilar:

✦ ***Renflexis (infliximab-abda) was approved on April 24, 2017.***

✦ ***Ontruzant (trastuzumab-dttb) was approved on Jan. 21, 2019.***

✦ ***Eticovo (etanercept-ykro) was approved on April 27, 2019.***

✦ ***Hadlima (adalimumab-bwwd) was approved on July 23, 2019.***

For the Managed Care Biologics and Injectables Index: Q4 2020, between Dec. 2, 2020, and Jan. 7, 2021, Zitter Insights polled 40 commercial payers with 130.8 million covered lives about Lucentis and Eylea biosimilars. Respondents with more than three-quarters of lives said they were likely to prefer biosimilars over their reference product (see chart, p. 4). Payers covering 57% of lives said they would cover ocular biosimilars separately from the brand drugs once two biosimilars were available.

Zitter Insights and AIS Health are both MMIT companies.

During the same time period, Zitter Insights polled 52 retinologists on their expected prescribing once biosimilars were available. Sixty-two percent of respondents said they were likely to prescribe a biosimilar Eylea over the reference drug, and 58% said they likely would prescribe a biosimilar Lucentis over the brand drug.

Some Factors Could Slow Uptake

Still, a few factors could impact Byooviz's uptake in the U.S. One is that "the dosing interval for Byooviz is more frequent at four to six weeks, compared to Eylea at eight to 12 weeks and potential candidates in the pipeline such as Lucentis PDS [i.e., port delivery system] at six months and [Roche's] faricimab at up to 16 weeks," explains Anderson, who adds that an FDA decision is due on Lucentis PDS for wet AMD by Oct. 23 and for faricimab for wet AMD and diabetic macular edema (DME) by January 2022. The FDA also has accepted the application for faricimab in diabetic retinopathy (DR), she notes.

In addition, Byooviz has approval for only three of Lucentis' five FDA-approved indications. It was not approved for DR and DME. Asked if Samsung Bioepis applied for those two indications, Kim responds that Byooviz is approved for its three indications as a single-use 0.5 mg (0.0 5mL of 10 mg/mL solution) vial, the same as Lucentis. For DME and DR, Lucentis is approved for a different dose: 0.3 mg (0.05 mL of 6 mg/mL solution).

The lack of approval for those two indications could slow uptake of the drug, says Lynn Nishida, R.Ph., head of clinical operations at Evio. However, Mesfin Tegenu, R.Ph., CEO of RxParadigm, points out that Byooviz has approval to treat wet AMD, which is "one of the most frequent retinal degenerative diseases." According to ResearchAndMarkets.com between 11 million and 15 million people in the U.S. have AMD, and about 1.7 million of those have wet AMD, which is the No. 1 cause of blindness in people more than 50 years old.

Belazi says estimates show that DME and DR make up only about 25% of Lucentis use.

Kinyua also notes that Byooviz has been studied in DR and DME and that the European Medicines Agency approved Byooviz for those indications "based on the totality of clinical evidence," which may influence how the agent is used in the U.S.

Brand Marketing May Stress Indications

Rayburg points out that all of Byooviz's indications are for the treatment of eye disorders, and since it "was proven to be both safe and effective for three of the indications, I really am not sure if this [i.e., not having the DME and DR indications] will make a big difference. It will, however, make a big difference to the brand competitor products, and I expect it will be an important part of the marketing message to support the use of those brand products over the use of this biosimilar." Providers also may choose to prescribe it off-label as they do for cancer drug Avastin, which has undergone clinical trials in eye disorders, but Genentech has never sought FDA approval for them.

Another differentiation between Byooviz and Lucentis (as well as Eylea) is that the biosimilar is available as a single-use vial, while the innovator product is available both in that format and in a prefilled syringe. Asked if

there is a prefilled syringe in development for Byooviz, Kim says that Samsung Bioepis is "unable to comment on the PFS at this moment."

Industry sources are divided on how much of a difference this makes. According to Belazi, "studies comparing the administration of Lucentis vials and prefilled syringes have demonstrated that the PFS does reduce preparation times and simplify the preparation procedures. In one study arm, the mean total duration of all syringe preparation steps was 46 seconds with the PFS vs. 75 seconds with the vial. In another, [it was] 46 seconds vs. 63 seconds.

"This equates to a 27%-39% time reduction when using the PFS rather than the vial," he continues. "The PFS does reduce injection time by a few seconds. However, there are additional advantages, including possible reduced risk of contamination, reduction in intraocular air bubbles and silicone oil droplets, and improved precision in the volume and the dose of intravitreal medication being administered. While all of these factors make the Byooviz vial less attractive for ophthalmologists to administer, it is unlikely to impact the uptake of Byooviz."

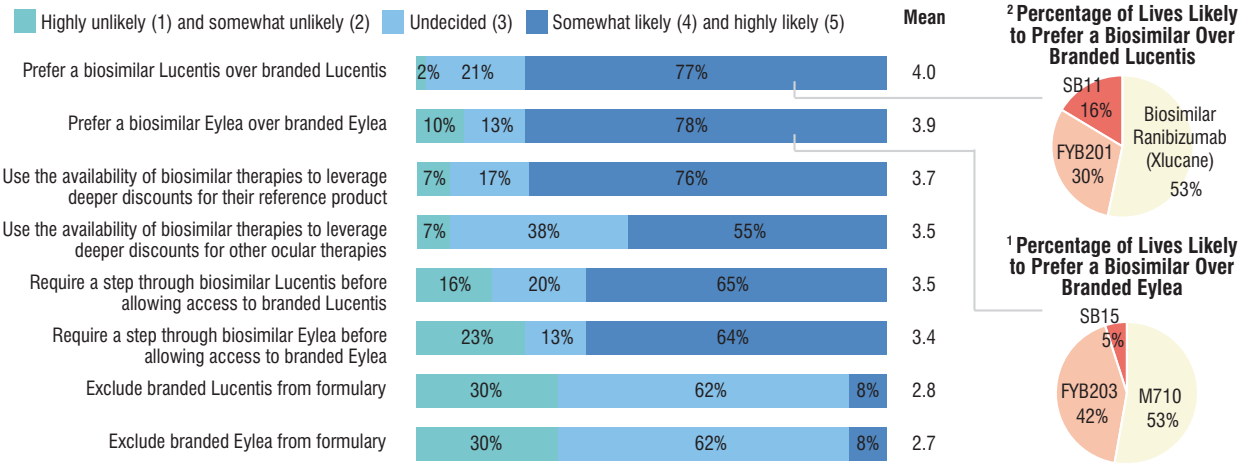
"It comes down to a matter of convenience," as well as sterility, says Wong. "Although the incidence of eye infections is less than 5% (as quoted to me by a retinal specialist), it still remains a concern. In short, in the face of similar pricing, I believe being only in a vial will impact uptake."

Ultimately, says Tegenu, uptake of the biosimilar "would probably be more dependent on whether the products are covered by the payer or if there is a preferred or nonpreferred status."

Perhaps most importantly, ophthalmologists have not had experience with biosimilars, which also could hamper the drugs' use. Payers have time, though, ahead of Byooviz's potential June 2022 launch, to address this issue.

"Unlike other specialists who have had the advantage of using biosimilars more regularly (e.g., rheumatologists, gastroenterologists, oncologists), ophthalmologists have very little experience with biosimilars, and it will take some time for them to become familiar with treating patients with a biosimilar," states Nishida. Payers' "key areas of focus should be on prescriber education and outreach to glean their insights as well as discuss/gauge their acceptance or willingness to prescribe biosimilars, if not for Lucentis, but also for other biosimilars that are anticipated to become available soon."

Anticipated Management Actions of Eylea/Lucentis Assuming U.S. Launch of Pipeline Biosimilar Therapies by Percentage of Covered Lives



Payers (Commercial) N = 40, Covered Lives N = 130.8 million
[1] Payers (Commercial) n = 26, Covered Lives n = 101.5 million;
[2] Payers (Commercial) n = 25, Covered Lives n = 101.0 million
Q: "How likely is your organization to take the following management actions, assuming a US launch of all pipeline biosimilar therapies and interchangeability is established for all agents?"
Q: [1] "Which biosimilar Eylea is your organization most likely to prefer over branded Eylea?"
Q: [2] "Which biosimilar Lucentis is your organization most likely to prefer over branded Lucentis?"

Similar data reported for the Medicare line of business
Surveys collected 12/02/2020 – 01/07/2021

SOURCE: Zitter Insights, Managed Care Biologics and Injectables Index: Q4 2020.

"As familiarity and confidence in biosimilars increase, so will utilization," asserts Belazi. He says that "to drive biosimilar adoption, they [i.e., payers] should proactively educate providers and patients on biosimilars. Ophthalmologists need to be educated on the regulatory approval pathway, clinical trial foundations and the interchangeability nuances of biosimilars."

The first move payers need to make is to "talk to their retina specialist to first determine if they are educated on the biosimilar evaluation process, as well as their comfort level with using a biosimilar," Wong says, pointing out that it took "several years" for oncologists to become comfortable with using biosimilars.

Payers Can Take Steps to Prepare

In addition, before Byooviz comes to market, "payers would generally want to consider their current medical policy for the therapeutic class, total utilization and conduct formulary management strategies to control costs and ensure access to patients," says Tegenu.

Step therapy, prior authorization, site-of-care optimization and quantity limits are crucial in keeping costs down, says Anderson. "Payers and specialty pharmacies should also strategize innovative programs focused on opportunities to further prevent waste, improve adherence and reduce overall spending."

Payers also should conduct "forecast modeling of when it makes the most sense to embrace biosimilars like Byooviz that will drive price competition," Nishida maintains.

"It is important for payers to have insight into their data, specifically the utilization and cost of all of these products, including the new biosimilar," recommends Rayburg. "They will also need to factor in any contracting and/or rebate options available per product and position them to prefer the lowest net cost product(s)."

"It will be necessary to have early payer engagement and education to facilitate sound clinical and financial formulary decisions," says Belazi. "Also, access to ophthalmic biosimilars like Byooviz via preferred formulary placement and step therapy strategies can promote biosimilar utilization."

"Payers need to start playing the chess game early," maintains Wong. "They need to start talking to the innovators to determine what their strategy will be, or not be, to maintain market share. They need start talking to Biogen to try to get a feel with what the list price will be and if there will be any discounting to try to make a dent upon the market.…They need to look at the nAMD and DME pipeline to determine if the need for current anti-VEGF therapy will remain."

More Biosimilars Are in Pipeline

Multiple biosimilars for both Lucentis and Eylea are in the late-stage pipeline.

On Oct. 1, Coherus BioSciences, Inc. said that the FDA had accepted its Biologics License Application (BLA) for CHS-201 (also known as FYB201), a Lucentis biosimilar candidate, from its partner, Bioeq AG. Coherus acquired U.S. commercial rights to the drug — which has an FDA action date of Aug. 2, 2022 — from Bioeq AG in 2019.

According to the most recent U.S. Biosimilar Report from AmerisourceBergen, updated Sept. 23, there are two Lucentis biosimilars, one of which is Xlucane. On July 27, 2021, Xbrane Biopharma AB said that Xlucane had met its primary endpoint demonstrating equivalent efficacy in its Phase III trial and that it plans to submit a BLA to the FDA in fourth-quarter 2021.

The report also shows that seven Eylea biosimilars are in Stage III trials. One of those is SB15, which Biogen and Samsung Bioepis are developing. On June 30, 2020, Samsung Bioepis said it had started a Phase III clinical trial; company spokesperson Kim confirms that trial is ongoing. "While we are unable to make predictions on the next clinical or regulatory milestones, we will endeavor to bring this important medicine to the market soon," she says.

Eylea Could See Competition in 2024

Belazi says that Eylea biosimilars could come onto the U.S. market as soon as 2024. Those products "are expected to be more impactful than Lucentis biosimilars. Eylea currently has over $5 billion in annual sales, and Lucentis has just over $2 billion in annual sales."

"In general, biosimilar uptake in the U.S. has steadily picked up steam over the past several years for many reasons, including increased prescriber confidence and familiarity with biosimilars, practical administrative/billing with separate codes and payment rates to differentiate products and payment schedules that encourage their use" and their lower costs, which help drive down their reference drugs' prices, says Nishida.

"In our experience, we have seen the entrance of additional biosimilars drive costs down for all products, including the brand innovator products," Rayburg tells AIS Health. "The presence of additional biosimilars creates additional competition and should continue to drive a decrease in costs for all products."

For more information on the Zitter data, contact Jill Brown Kettler at jbrown@aishealth.com.

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Groups Warn Against Avastin Biosimilar Off-Label Use in Eyes

Biosimilars are finally starting to bring down the prices of their innovator products across a range of indications, research shows. The FDA often approves biosimilars across some or all of the innovator drug's indications even if applicant companies have not conducted studies in those uses. But two professional societies have been pushing back against payers' allowance of two Avastin (bevacizumab) biosimilars in untested ocular indications.

Roche Group unit Genentech USA, Inc.'s Avastin is commonly used off-label in ophthalmic indications (see story, p. 1). The drug, first approved in 2004, has undergone clinical trials supporting its use in eye disorders, but Genentech has not filed for FDA approval in those indications. This use requires the drug to be compounded and repackaged — and because this is a much lower dose than the drug's oncology doses, it costs about $50 per injection, compared with thousands of dollars for the vascular endothelial growth factor (VEGF) inhibitors approved for eye diseases.

The FDA has approved two Avastin biosimilars — Amgen Inc.'s Mvasi (bevacizumab-awwb) and Pfizer Inc.'s Zirabev (bevacizumab-awwb) — for multiple oncolytic indications. Various payers also cover all three bevacizumab products off-label in ophthalmic indications. But while Avastin has undergone clinical trials supporting its use in eye disorders, the two biosimilars have not.

The American Society of Retina Specialists (ASRS) and the American Academy of Ophthalmology (AAO) are warning that the biosimilars may damage people's vision, particularly Zirabev, which is prepared with edetate disodium dihydrate (EDT), an agent that "has demonstrated toxicity to corneal and conjunctival epithelial cells. Potential retinal toxicity of EDTA has not been studied."

Groups Have Been Contacting Payers

ASRS and AAO have been conducting outreach to multiple payers and CMS about this "inappropriate use" of the biosimilars "without a prior clinical trial in eye disease and testing for retinal toxicity."

At least one FDA-registered 503B outsourcing facility is advertising Mvasi for ophthalmic use. Edge Pharma, which is licensed to sell to all U.S. states except Alabama and Virginia, offers the ability to order the drug online.

A spokesperson for Pfizer tells AIS Health, a division of MMIT, that the company doesn't comment on off-label use of its products. However, a Pfizer product monograph on Zirabev states that the drug "is not formulated and has not been authorized for intravitreal use." Such use may result in "serious ocular adverse events," including blindness.

An Amgen spokesperson says that "Amgen recommends use of Mvasi consistent with its label. Mvasi is not FDA-approved to treat macular degeneration."

Avastin Shortage Triggered Issue

Earlier this summer, an Avastin shortage was triggered by a supply chain issue in which a major supplier of the drug "initiated an indefinite halt on the distribution of all bevacizumab syringes."

ASRS and AAO initially conducted outreach to payers asking them not to require Avastin as a first step in the treatment of eye diseases and to provide coverage for the other branded non-bevacizumab VEGF inhibitors approved for eye diseases. Then that outreach shifted to focus on requesting that payers not encourage the use of the biosimilar forms of Avastin as alternatives to the innovator product in the treatment of eye diseases.

"All of the major payers have Mvasi and Zirabev listed as ocular alternatives," the AAO tells AIS Health. At least one, UnitedHealthcare, has responded to the outreach by removing Mvasi and Zirabev from coverage under its ophthalmologic policy for VEGF inhibitors. As of early October, AAO says that is the only plan that has changed its policy. "The Academy is in the process of scheduling meetings with CVS Health and Aetna on this issue," it says.

Asked if CMS has taken any action, the AAO says that it and ASRS "met with [CMS acting Deputy Administrator & Director and Deputy Director] Cheri Rice and staff at CMS to discuss the issue. CMS took the meeting seriously and are internally discussing next steps. We hope to have follow-up from CMS soon."

Other facilities have increased production of compounded Avastin, addressing the supply issue. But "while the supply of Avastin seems to be stable at the moment, there is a concern that when informed of potential supply issues, as occurred earlier this summer, plans may consider suggesting that an Avastin biosimilar may be used in its place," Charles Wykoff, M.D., Ph.D., chair of the practice management committee at ASRS, tells AIS Health. "Beyond supply issues, we are concerned that plans including Medicare Advantage plans are inappropriately including Avastin biosimilars in their anti-VEGF policies in general."

According to Wykoff, "inclusion of these biosimilars is contrary to sound clinical evidence and FDA-approved labeling of these products. To be clear, we are not aware of any plans that are requiring Avastin biosimilars prior to use of Avastin as part of step therapy, but some…are encouraging their use."

ASRS Also Points to Prior Experience

ASRS's position, he says, is based on lack of evidence for the biosimilars, as well as "experiences with prior products, including the first version of Lucentis that was lyophilized and caused inflammation in some eyes and more recently Beovu," which was "found to lead to severe retinal vasculitis in a small proportion of patients." The cause of this event is under investigation, he adds.

"ASRS does not oppose the use of biosimilars in general, but there should be clinical evidence of their safety and efficacy before ophthalmic use," he maintains.

Contact AAO via www.aao.org and Wykoff via Lydia Steck at lydia.steck@asrs.org. ✧

Walgreens Makes Majority Investment in Shields Health

Walgreens Boots Alliance recently revealed that it is making a majority investment in Shields Health Solutions through its subsidiary Walgreen Co. The deal will expand Walgreens' position within the growing hospital-based specialty pharmacy space.

Shields is a specialty pharmacy integrator that partners with health systems to help them create and grow a hospital-owned specialty pharmacy program. The hospitals own the pharmacies while Shields manages them.

Company Made Minority Investment in '19

Walgreens made a minority investment of 23% in Shields in July 2019; the more recent arrangement — an approximately $970 million investment — will give Walgreens 71% ownership of Shields, with an option to purchase the remaining interests. Shields will continue to operate as a distinct brand and entity under its current leadership.

Welsh, Carson, Anderson & Stowe is a Shields investor; Hg Capital Partners and WCAS share control of MMIT, the parent of AIS Health.

Earlier this year, Shields unveiled a deal to purchase ExceleraRx Corp., which is a network of specialty pharmacies among integrated delivery networks and academic medical centers. Following the acquisition, Shields represents more than 1 million specialty patients in the U.S. across more than 30 disease states and has more than 70 health system partners.

That "larger market share surely made Shields Health more attractive to Walgreens," says Elan Rubinstein, Pharm.D., M.P.H., principal at EB Rubinstein Associates. In addition, based on a Shields LinkedIn job posting for vice president of 340B optimization, he surmises that the 340B Drug Pricing Program "is an area of interest for Shields. Since 340B is a fast growth area nationally, this is likely of major interest to Walgreens."

Bill Sullivan, a longtime industry consultant and executive editor of the Anton Rx Report, wrote in that blog on Sept. 23 that "in 2019 WAGS likely saw the writing on the wall….. that hospitals would eventually wise up and open their own specialty pharmacies to recoup lost revenue. WAGS has a history of working with hospitals opening a number of on-campus pharmacies in recent years. The Shields model fit that strategic mindset.... which likely prompted the initial investment. The ExceleraRx acquisition gave the model some serious traction, so this week's move is less surprising. Last thought…. tactically, WAGS has ensured that they will be at the table with many very influential hospitals, payers, and manufacturers. That's a good place to be."

Firm May Acquire Remaining 29% Soon

"The additional 48% ownership stake allows WBA to further benefit from Shields's penetration into the health system-based specialty care model with its focus on a higher-touch care model and reducing overall healthcare costs for those patients," wrote Elizabeth Anderson, an Evercore ISI analyst in a Sept. 21 research note. She wrote that "we would expect" Walgreens to acquire the remaining 29% ownership "in the next year or two."

The deal does not impact Walgreens' specialty pharmacy relationship with Prime Therapeutics LLC, she added.

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JAK Inhibitors Will Update Labels

continued from p. 1

The agency recommends that anyone on one of these therapies "should tell your health care professional if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put you at higher risk for serious problems with the medicines. Patients starting these medicines should also tell your health care professional about these risk factors." The FDA says it will require changes to "several sections" of the drugs' prescribing information and patient medication guides.

While Olumiant and Rinvoq were not studied, they have the same mechanism of action as Xeljanz, so the FDA says they might have similar risks.

New FDA Specialty Approvals

✦ ***Sept. 15: The FDA granted another indication to BeiGene, Ltd.'s Brukinsa*** (zanubrutinib), giving it accelerated approval for the treatment of people with relapsed or refractory marginal zone lymphoma following treatment with at least one anti-CD20-based regimen. The agency first approved the drug on Nov. 14, 2019. The recommended dose of the capsule is 160 mg twice daily or 320 mg once daily. Website Drugs.com lists the price of 120 80 mg capsules as more than $14,094.00.

✦ ***Sept. 15: The FDA gave accelerated approval to Takeda Pharmaceutical Company Ltd.'s Exkivity*** (mobocertinib) for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations as detected by an FDA-approved test (see brief below) whose disease has progressed on or after platinum-based chemotherapy. Dosing is 160 mg via four 40 mg capsules once daily. The price of 120 40 mg capsules is $25,000.00.

✦ ***Sept. 15: The FDA gave another indication to Thermo Fisher Scientific's Oncomine Dx Target Test*** as a next-generation sequencing companion diagnostic for Exkivity to identify people with NSCLC with EGFR exon 20 insertion mutations (see brief above). The agency initially approved the companion diagnostic on June 22, 2017.

✦ ***Sept. 17: The FDA expanded the label of Exelixis, Inc.'s Cabometyx*** (cabozantinib) to treat people at least 12 years old with locally advanced or metastatic differentiated thyroid cancer that has progressed following vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible. The agency first approved the drug on April 25, 2016. The recommended dose is 60 mg once daily and 40 mg once daily in pediatric patients with a body surface area less than 1.2 m^2. Drugs.com lists the price of 30 tablets for all three doses — 20 mg, 40 mg and 60 mg — as $22,625.46.

✦ ***Sept. 20: The FDA approved Samsung Bioepis Co., Ltd. and Biogen Inc.'s Byooviz*** (ranibizumab-nuna) for the treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV). The biosimilar of Roche Group unit Genentech USA, Inc.'s Lucentis (ranibizumab) is the first ophthalmology biosimilar that the agency has approved. Recommended dosing for wet AMD and RVO is every 28 days via an intravitreal injection, while dosing for mCNV is every 28 days for up to three months, with re-treatment if needed. Samsung Bioepis and Biogen will be able to market the therapy in the U.S. in June 2022.

✦ ***Sept. 20: The FDA gave accelerated approval to Seagen Inc. and Genmab A/S's Tivdak*** (tisotumab vedotin-tftv) to treat adults with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Recommended dosing of the antibody-drug conjugate is 2 mg/kg, up to a maximum of 200 mg, via a 30-minute intravenous infusion every three weeks. The drug's price is $5,885.00 per 40 mg single-dose vial or about an average monthly price of $34,000.00.

✦ ***Sept. 21: The FDA approved Incyte Corp.'s Opzelura*** (ruxolitinib) for the short-term and non-continuous treatment of mild-to-moderate atopic dermatitis in non-immunocompromised people at least 12 years old whose disease is not adequately controlled with topical prescription therapies or when those treatments are not advisable. Recommended dosing is a thin layer of the cream twice daily to affected areas of up to 20% of the body's surface. The price of one tube is $1,950.00, and the company expects people to use three to four tubes per year.

The FDA noted that it has approved two other JAK inhibitors: Incyte Corp.'s Jakafi (ruxolitinib) and Bristol Myers Squibb's Inrebic (fedratinib).

But because they are not indicated for inflammatory conditions, they do not have to update their prescribing information.

This isn't the first time that the agency has warned about safety concerns with Xeljanz. On Feb. 5, 2019, the FDA issued a safety announcement around a clinical trial finding that showed people with RA on a 10-mg-twice-daily dose were at increased risk of blood clots in their lungs and death. The agency noted that it had approved this dosing regimen only in ulcerative colitis, not RA. On July 26, 2019, the agency issued another safety announce-

New FDA Specialty Approvals *(continued)*

- ***Sept. 22: The FDA expanded the label of Incyte's Jakafi*** (ruxolitinib) to include the treatment of chronic graft-versus-host disease after failure of one or two lines of systemic therapy in people at least 12 years old. The agency initially approved the tablet on Nov. 16, 2011. The starting dose for the newest indication is 10 mg twice daily and can be adjusted based on safety and efficacy. Drugs.com lists the price of 60 tablets for all five doses — 5 mg, 10 mg, 15 mg, 20 mg and 25 mg — as $15,412.68.

- ***Sept. 24: The FDA gave two additional indications to Amgen Inc.'s Repatha*** (evolocumab): (1) as an add-on treatment to diet and other low-density lipoprotein cholesterol-lowering therapies for people at least 10 years old with heterozygous familial hypercholesterolemia to reduce LDL-C and (2) as an adjunct to other LDL-C lowering therapies for the treatment of homozygous familial hypercholesterolemia in people at least 10 years old. The agency initially approved the PCSK9 inhibitor on Aug. 27, 2015. Recommended dosing is 420 mg per month by subcutaneous injection. The drug's monthly wholesale acquisition cost is $476.55.

- ***Sept. 28: The FDA approved a new indication for Eli Lilly and Co.'s Erbitux*** (cetuximab) in combination with Pfizer, Inc.'s Braftovi (encorafenib) to treat adults with metastatic colorectal cancer with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy. The agency first approved the drug on Feb. 12, 2004. Dosing is a 120-minute intravenous infusion of Erbitux 400 mg/m^2, followed by a 60-minute infusion 250 mg/m^2 weekly and 300 mg once daily of Braftovi. Drugs.com lists the price of 2 mg/mL of Erbitux as more than $733.00 and 120 75 mg capsules of Braftovi as more than $13,243.00.

- ***Sept. 29: The FDA approved Mirum Pharmaceuticals, Inc.'s Livmarli*** (maralixibat) for the treatment of cholestatic pruritus in people at least 1 year old with Alagille syndrome. The ileal bile acid transporter (IBAT) is the first and only FDA-approved drug for this indication. Initial dosing for the oral solution is 190 mcg/kg once daily and then increased to 380 mcg/kg once daily after one week. The drug is priced at around $391,000.00 per year for the average patient.

- ***Oct. 1: The FDA gave another indication to Gilead Sciences, Inc. division Kite Pharma, Inc.'s Tecartus*** (brexucabtagene autoleucel) for the treatment of people at least 18 years old with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The chimeric antigen receptor T-cell (CAR-T) initially was approved July 24, 2020. One-time dosing for the newest use is 1 x 10^6 CAR-positive viable T cells per kg of body weight with a maximum of 1 x 10^8 CAR-positive viable T cells. The therapy's price is $373,000.

- ***Oct. 8: The FDA approved ChemoCentryx, Inc.'s Tavneos*** (avacopan) as an adjunctive treatment for adults with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, specifically granulomatosis with polyangiitis and microscopic polyangiitis, in combination with standard therapy. The recommended dose is 30 mg via three 10 mg capsules twice daily. The drug will have a wholesale price of between $150,000 and $200,000, according to Reuters.

- ***Oct. 8: The FDA approved Sumitovant Biopharma Ltd. subsidiary Enzyvant Therapeutics GmbH's Rethymic*** (allogeneic processed thymus tissue-agdc) for the treatment of pediatric patients with congenital athymia. Dosing is patient-customized, and the processed tissue is surgically implanted, with a recommended dose range of 5,000 to 22,000 mm^2 of Rethymic/m^2 recipient body surface area.

ment, disclosing that it had approved a black box warning around this risk for Xeljanz's label.

The FDA initially approved Xeljanz as a tablet on Nov. 6, 2012, for the treatment of adults with moderately to severely active RA who have an inadequate response or intolerance to methotrexate. It's now approved for three additional inflammatory conditions: for adults with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs), for adults with moderately to severely active ulcerative colitis who have had an inadequate response or who are intolerant to TNF inhibitors and for active polyarticular course juvenile idiopathic arthritis in people at least 2 years old as an oral solution. An extended-release Xeljanz XR tablet also is available.

Drugs Are Seeing FDA Decision Delays

While the FDA was reviewing the Xeljanz data, it also delayed decisions on additional anti-inflammatory indications for currently marketed JAK inhibitors, as well as ones with initial applications at the agency. Decisions on Olumiant in atopic dermatitis, Xeljanz in ankylosing spondylitis and Rinvoq in atopic dermatitis, psoriatic arthritis and ankylosing spondylitis have been delayed throughout the year, as has the application for Pfizer's abrocitinib in atopic dermatitis.

One anti-inflammatory JAK inhibitor, however, recently gained FDA approval following a delayed agency decision in June: Incyte's Opzelura (ruxolitinib). On Sept. 21, the agency approved the drug — which is a topical version of Jakafi — for the short-term and non-continuous treatment of mild-to-moderate atopic dermatitis in non-immunocompromised people at least 12 years old whose disease is not adequately controlled with topical prescription therapies or when those treatments are not advisable (see brief, p. 8). The product also has a black box warning around safety issues seen among JAKs used for inflammatory conditions.

Jakafi also received an additional indication on Sept. 22, but that was for chronic graft-versus-host disease (see brief, p. 8).

Source: FDA Takes Conservative Stance

Opzelura's labeling "implies that the safety issues associated with JAK inhibitors goes beyond the systemic route of administration (e.g., injectables and orals) for these products," says Lynn Nishida, R.Ph., head of clinical operations at Evio. "And with even topical administration and acute treatment with a JAK inhibitor, the FDA is likely to err on the conservative side and view this as a class issue in requiring similar box warnings for cancer and cardiovascular risks regardless of how it's administered."

Opzelura has a "somewhat narrow and restrictive label," says Dea Belazi, Pharm.D., M.P.H., president and CEO of AscellaHealth. In addition to its short-term use in the mild-to-moderate setting, the label advises against its use with certain other agents. With its limits on use, the drug "will not likely be a therapeutic first-line option."

"Given there is a difference in systemic exposure with ruxolitinib cream vs. oral JAKs, approval of ruxolitinib does not shed much light as to the fate of the oral JAKs seeking an indication for" atopic dermatitis, says Robert Kinyua, Pharm.D., senior director of clinical program development at Prime Therapeutics LLC. "Additionally, ruxolitinib is for mild-to-moderate disease while oral JAKs were evaluated for moderate-to-severe disease, meaning the risk vs. benefit considerations are different between the cream and oral JAKs."

Renee Baiano, Pharm.D., C.S.P., clinical program manager at AllianceRx Walgreens Prime, says it's possible that the FDA could approve some JAK inhibitors in more severe inflammatory diseases but reject others in less severe inflammatory conditions. "A risk vs. benefit analysis is an important part of all new drug approvals," she says.

According to Kinyua, if those drugs are approved, "they will likely be indicated for those with moderate-to-severe disease. What the FDA might do is require that they are used after failure of safer agents."

Agency Has Been Under Scrutiny Lately

In treating the Xeljanz data as a class effect, Winston Wong, Pharm.D., president of the W-Squared Group, says he can't say whether the FDA is being "overly cautious,…but given the amount of scrutiny they have been under lately since the approval of aducanumab, can you blame them?

"What is unknown, and in my opinion requires further investigation, is whether there is a difference in incidence based upon the specificity of the four JAK receptors being inhibited, as well as the strength of the inhibition," he continues. And "should the warning be applied to the bone marrow disorders as well? Bottom line is that as the FDA sorts out the risk of adverse events, the current JAK inhibitors standing before the FDA for approval will most likely be delayed and, when approved, will most likely carry the 'class' black box and indication."

For the Managed Care Biologics and Injectables Index: Q2 2021, between May 18, 2021, and July 13, 2021, Zitter Insights polled 40 com-

mercial payers with 129.5 million covered lives about the earlier study of the higher Xeljanz dose and its impact on their management of psoriatic arthritis and of the JAK/STAT inhibitors. Payers with almost 50% of covered lives said the study was highly influential.

Zitter Insights and AIS Health are both MMIT companies.

During the same time period, Zitter Insights polled 50 rheumatologists on how the study would impact their prescribing. They reported a higher impact than payers, with 64% saying it was highly influential on their psoriatic arthritis prescribing, and 56% said the same for JAK/STAT inhibitors.

The FDA's action "in general… will cause pause by prescribers and patients for treatment with any of these" JAK inhibitors, says Nishida. "To that end, there will be ongoing dissension on whether topical Opzelura should have been included with systemic JAK inhibitors in receiving the same black box warning or not."

Source: Patients Need Re-evaluation

"Current patients on JAK inhibitors should be re-evaluated to ensure that the patient is receiving an optimal drug therapy regimen for their medical condition," asserts Belazi.

With the JAKs in inflammatory conditions, "payers need to construct their coverage policies to identify patients who may best benefit vs. when use may pose risk," recommends Nishida. "It comes down to identifying unique situations of a patient's medical circumstances and risks, realizing that we cannot treat everyone the same way with a one-size-fits-all medication treatment." Using traditional utilization management tactics, as well as technology available at the point of prescribing, payers can "identify patients with comorbid conditions that may contribute to exacerbation of adverse events and the patient's ability to tolerate the medications," she explains.

In general with the inflammatory conditions, "most payers have selected one or two products to represent different mechanisms of action," says Nishida. "Very rarely would there be step therapy that required a JAK inhibitor before a TNF. Most payers recognize by medical policies the unique safety profiles for TNFs and JAK inhibitors and criteria that allows exceptions to be made for nonpreferred products because of patient individual circumstances and risk factors."

Plans May Need to Alter Prior Auth

Plans, however, that placed the JAK inhibitors — which have a "slightly lower" cost than the TNF inhibitors before rebates — on par with the anti-TNFs will need to change their prior authorization criteria, states Wong.

Kinyua notes that the updated labels have not yet been published, and payers' actions "will be heavily influenced by the language" in those labels.

In managing the JAK inhibitors in inflammatory conditions, Theresa James, Pharm.D., C.S.P., sales solutions director at AllianceRx Walgreens Prime, advises that payers "stay the course — most, if not all, payers currently require step therapy and/or prior authorizations for approval of JAK inhibitors for inflammatory indications." Kinyua notes that guidelines do not recommend using JAKs before TNF inhibitors.

In addition to step therapy and prior authorization, James says that quantity limits are another strategy payers can implement to make sure the JAK inhibitors are used in the second-line setting.

According to James, "due to the updated warnings and restrictions limiting the use of JAK inhibitors to second-line therapy, utilization is expected to decline."

The TNF inhibitors class is well-established in the U.S., with Remicade (infliximab) from Janssen Biotech, Inc., a Johnson & Johnson company, first gaining approval on Aug. 24, 1998, for Crohn's disease, followed by Amgen Inc.'s Enbrel (etanercept) approval on Nov. 2, 1998, for RA and then Humira (adalimumab) for RA on Dec. 31, 2002. UCB, Inc.'s Cimzia (certolizumab pegol) was approved for Crohn's on April 22, 2008, and Janssen's Simponi (golimumab) for RA, psoriatic arthritis and ankylosing spondylitis on April 24, 2009.

Anti-TNFs May Not Work in Everyone

"While TNF inhibitor medications are good options with well-established safety profiles, not all patients respond or tolerate this class of medication," says Baiano. "For example, about 20% to 40% of RA patients treated with a TNF inhibitor fail to achieve a 20% improvement according to criteria set out by the American College of Rheumatology."

Belazi notes that among people initially responding to a TNF inhibitor, "secondary loss of response may prompt discontinuation of treatment in up to 50% of patients after 12 months on therapy. In RA, it was found that up to one-third of patients showed poor response to this treatment." In addition, "anti-TNF agents are generally well tolerated, but it may also depend on the disorder. A comparison of two prospective safety cohorts of patients with RA and psoriasis found a much lower rate of serious adverse/mortal events in the psoriasis group compared to the RA group.

Patients with RA had higher rates of infections, cardiac/respiratory disorders and infusion reactions (higher use of infliximab), while those with psoriasis had more skin/subcutaneous and hepatobiliary disorders."

Because Jakafi and Inrebic were not included in the labeling updates, changes in payer management of those therapies is not expected, as it was already common practice to require prior authorization for these medications, says Jill Distad, Pharm.D., B.C.G.P., sales solutions director at AllianceRx Walgreens Prime. However, "ultimately…these drugs will likely be viewed by payers and providers through a different lens moving forward."

Asked if payers should be reaching out to members and providers about the FDA warning, Distad replies that "it's best practice for payers to make providers (both prescribers and pharmacies) aware when the FDA issues Drug Safety Communications. As for member outreach, payers certainly don't want to cause the patient any distress or concern. Patients and providers should discuss the safety of the drug and whether or not it is an appropriate treatment. Payers and pharmacies both should be prepared to answer questions from concerned members, always ensuring them it's best to follow up with their provider to further discuss their course of treatment."

"This is a black box warning; thus, I do believe patients should be notified," says Wong. "This message should be clear that the FDA has identified the risk of serious adverse effects; however, they should not stop taking their medication without first consulting their physician. Health plans should also be providing a list of patients to whom they had prescribed a JAK inhibitor for an immunologic condition."

Belazi agrees that payers should reach out to providers over the JAKs' safety risks to "help reinforce their education regarding the adverse events seen with this class of drugs and to ensure appropriate use of this class of drugs for their patients." In addition, reaching out to members on one of these drugs "is also encouraged and will help patients consult with physicians on the appropriate treatment course for the patient."

For more information on the Zitter data, contact Jill Brown Kettler at jbrown@aishealth.com.

Contact Baiano, Distad and James via Adrienne Foley at Adrienne.foley1@alliancerxwp.com, Belazi through Caroline Chambers at cchambers@cpronline.com, Kinyua through Karen Lyons at KLyons@primetherapeutics.com, Nishida at lynn@evio.com and Wong at w2sqgroup@gmail.com. ✧

News Briefs

✦ ***Over the past five years, biosimilars created competition that resulted in savings of $9.8 billion***. That's according to Amgen Inc.'s 2021 Biosimilar Trends Report, its eighth edition. The therapies also have the potential to save people out-of-pocket costs of $238 million in the nine classes in which the agents have been approved. The drugs are launching with wholesale acquisition costs that are generally between 15% and 37% less than those of their reference products.

✦ ***The average compound annual growth rate (CAGR) of biologics from 2015 to 2019 was 14.6%***, according to the 2021 Medication Access Report: Complex Care & Specialty Medications Edition from CoverMyMeds. That's compared with a CAGR of 1.6% for nonbiologics. From 2010 to 2015, the use of the buy and bill model for in-practice administration of therapies decreased 15 percentage points, while the use of white bagging increased 18 percentage points. More than half of people who are prescribed a specialty drug wait more than a week between the initial prescription and their first dose.

✦ ***A study by Moto Bioadvisors found that hospitals participating in the 340B Drug Pricing Program charge an average of 3.8 times their 340B acquisition prices for oncology drugs***. The report, which was commissioned by the Community Oncology Alliance, examined 52,180 hospital-reported prices for 59 cancer drugs that had the highest 2019 Medicare expenditures across 123 acute care 340B hospitals. That's the total number out of 1,087 acute care 340B disproportionate share hospitals that had published all the required price transparency data per a CMS regulation that went into effect Jan. 1, 2021.

✦ ***PEOPLE ON THE MOVE:*** Prime Therapeutics LLC named ***Chris Knibb*** chief financial officer (CFO). He recently held the CFO position at SOC Telemed. Prime also promoted its previous CFO, ***Dave Schlett***, to executive vice president – chief client relationship and administrative officer.