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# FDA Approves Dapagliflozin to Cut Risk of Hospitalization for Heart Failure in Type 2 Diabetes

MARY CAFFREY

**THE FDA TODAY** approved AstraZeneca's dapagliflozin (Farxiga) to reduce the risk of hospitalization for heart failure for patients with type 2 diabetes (T2D) and established cardiovascular disease or multiple cardiovascular risk factors.

The approval comes almost a year after presentation of results from the 17,000-patient DECLARE-TIMI 58 cardiovascular outcomes trial (CVOT), which showed that the sodium glucose co-transporter 2 (SGLT2) inhibitor significantly reduced hospitalization for heart failure and appeared to slow the loss of kidney function.

SGLT2 inhibitors work differently than other drugs for T2D by targeting a protein that normally causes the body to take excess glucose back up into the body; instead, excess glucose is expelled through the urine, thus keeping glycated hemoglobin in check. Besides its ability to prevent heart failure, the drug class has been shown to prevent renal decline.

Notably, AstraZeneca was the only manufacturer among the makers of the 3 major SGLT2 inhibitors sold in the United States to come away from a CVOT having met a primary endpoint that included heart failure. Researchers added a second composite primary endpoint of cardiovascular death and hospitalization for heart failure after the 2015 results for empagliflozin showed a 38% reduction in cardiovascular death and a 35% reduction in hospitalization for heart failure.

Results from DECLARE-TIMI were presented in November 2018 at the American Heart Association Scientific Sessions and published in the New England Journal of Medicine in January 2019.[1]

While results of SGLT2s on heart failure have been reported in other outcomes trials and in real-world studies—including a large study sponsored by AstraZeneca—the decision to expand DECLARE-TIMI 58 means that dapagliflozin is first to the finish line with a specific indication for reducing the risk of hospitalization for heart failure in certain patients with T2D.

**ALSO IN THIS ISSUE...**

Competitors empagliflozin (Jardiance) and canagliflozin (Invokana) have different cardiovascular indications, for reducing the risk of cardiovascular events. FDA has granted dapagliflozin Fast Track designation for an indication of reducing the risk of cardiovascular death for patients with heart failure with reduced ejection fraction or preserved ejection fraction, as well as Fast Track designation for a designation to prevent progression of renal failure, based on separate ongoing trials.

"DECLARE-TIMI 58 is a landmark trial, offering compelling evidence that dapagliflozin can reduce the risk of heart failure in patients living with type 2 diabetes with multiple risk factors for or established cardiovascular disease," said Stephen Wiviott, MD, of Brigham and Women's Hospital and Harvard Medical School, who led the study, in a statement.

"These data could help change the way we approach diabetes management—going beyond a singular focus on glucose control to help address the risk of heart failure in a diverse population of patients," he said. ■


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# Wasteful Drug Spending Contributes to High Prescription Costs

ALISON RODRIGUEZ

**RISING PRESCRIPTION DRUG** costs continue to place a financial burden on patients and employers; however, reducing the use of high-cost, low-value drugs on formularies could lower drug spending and out-of-pocket costs for enrollees, according to a brief published by The Commonwealth Fund.

The author, Lauren Vela, MBA, senior director of member value, Pacific Business Group on Health, aimed to identify drugs that add waste on employers' formularies, measure the savings from removing that waste, and identify the best practices in pharmacy benefit management.

"Large self-insured employers and other healthcare plan sponsors are concerned about rising prescription drug costs. Formularies developed on their behalf by intermediaries like pharmacy benefit managers (PBMs) and health plans can ensure drug safety and support negotiating with manufacturers," explained Vela. "But intermediaries can profit from these negotiations, creating financial incentives to include high-price drugs even if they offer little clinical value."

The research used data from 15 self-insured plan sponsors, 13 of which are members of the Pacific Business Group on Health, in order to analyze drug utilization and estimate the savings from reducing the use of drugs that cost more than their commensurate clinical value. In total, 868 drugs from 71 drug groups, making up 6% of claims, were classified as wasteful during the research.

The analysis demonstrated that reducing the use of high-cost, low-value drugs could lead to $63 million in annual savings among the 15 plan sponsors, which represents approximately 3% to 24% of overall pharmacy spending.

Additional findings included:

- Wasteful prescriptions represented 3% to 12% of total claims per sponsor evaluated, with an average savings of $413 per script
- Generic drugs made up 58% of wasteful prescriptions
- Brand-name drugs made up 42% of wasteful prescriptions, with an average savings of $682 per wasteful script

"These savings are compelling, given the relatively low administrative barrier to implementation. Nevertheless, adoption may be slow; plan sponsors make benefit decisions based on factors that might trump cost reduction," concluded Vela. "Better formulary management—including elimination of wasteful spending—can help plan sponsors provide their workers with access to appropriate and innovative medications at lower overall cost and ultimately improve health outcomes." ■

# OneOncology Has Begun Administering Bevacizumab, Trastuzumab Biosimilars

JAIME ROSENBERG

**WEEKS AFTER THE** first 2 anticancer biosimilars entered the US market, OneOncology announced that its partner practices have already started administering the drugs.

The 2 biosimilars, bevacizumab-awwb (Mvasi), referencing Avastin, and trastuzumab-anns (Kanjinti), referencing Herceptin, arrived on the market in July. At the time, the Amgen—Allergan partnership announced that the list price of both products would be 15% cheaper than their respective reference products.

"While biologics have made important and exciting progress treating some cancers, they have also come at a great financial cost," Jeffrey Patton, MD, president of physician services at OneOncology, explained in a statement. "Making Mvasi and Kanjinti preferred OneOncology Agents gives our physicians immediate access to cutting-edge therapies and reinforces our commitment to leading the oncology marketplace and delivering the highest-quality and most cost-effective care to our patients."

OneOncology, led by Tennessee Oncology, New York Cancer & Blood Specialists, and West Cancer Center, launched in September 2018 to help community oncology practices navigate the cancer care landscape and provide high-quality care to their patients.

In line with their quadruple aim of increasing access, improving quality, reducing costs, and transforming the patient experience, the partnership made the decision to make biosimilars preferred formulary agents as part of its cost effectiveness strategy.

"As we begin to incorporate biosimilar medications into our treatment pathways, we will collaborate with our physicians to navigate the fluctuating healthcare landscape and drive initiatives that ensure our clinicians appropriately utilize the right therapeutic sequence at the right time for the patient," said Lee Schwartzberg, MD, chief medical officer of OneOncology, in a statement.

Biosimilar stakeholders and advocates for the drugs will likely welcome the news, as estimates have projected up to $60 billion in savings in 2023 for a 5-year total of $153 billion as a result of biosimilar use. Just this week, Vizient released its semiannual drug pricing forecast, in which they said biosimilars will play a key role in mitigating rising spending on drugs among its membership.

However, stakeholders have argued that abuses of the patent system that delay biosimilar competition are costing biosimilar savings. To date, there have been 7 approved biosimilars for the treatment of cancer, and just Mvasi and Kanjinti have been launched. ■

# Medicare Beneficiaries May Pay More for Some Generics Than Brand-Name Drugs

LAURA JOSZT

**UNDER THE MEDICARE** Part D benefit, patients may actually spend more out of pocket (OOP) on generic drugs compared with brand-name drugs, according to a new study published in Health Affairs. This happens because of manufacturer discounts on brand-name drugs in the Part D coverage gap, researchers found.

They used data from the Medicare Formulary Files for the first quarter of 2018 and compared prices, formulary coverage, and projected annual OOP spending for Part D and stand-alone enrollees.

"For Medicare beneficiaries needing small-molecule specialty drugs or biologics, price differences between generics or biosimilars and their brand-name counterparts may be relatively modest, compared with traditional generic drugs," the

authors explained.

Since 2012, patients using brand-name drugs have reached the coverage gap with lower OOP spending because they were able to receive a manufacturer discount that counts toward OOP spending. The Bipartisan Budget Act (BBA) attempted to fix this, but while it modified the Part D benefit so patients did not pay more for biosimilars than for brand-name drugs, the law did not apply to generic drugs.

They used a sample of 9 brand-name drugs that have generics or biosimilars:

- Crestor versus rosuvastatin (traditional generic)
- Lantus versus basaglar (traditional generic)
- Abilify versus aripiprazole (traditional generic)
- Invega versus paliperidone (traditional generic)
- Remicade versus Inflectra (biosimilar)
- Neupogen versus Zarxio (biosimilar)
- Copaxone versus glatiramer (specialty generic)
- Nilandron versus nilutamide (specialty generic)
- Gleevec versus imatinib (specialty generic)

The authors found that before the BBA, biosimilars and specialty generics required higher OOP spending relative to brand-name drugs. The difference ranged from $591 for generic imatinib instead of brand-name Gleevec to $1949 for biosimilar Zarxio instead of brand-name Neupogen. Patients on biosimilar Inflectra were spending $4097 a year OOP compared with $2858 OOP for brand-name Remicade.

However, after the BBA, OOP spending for patients on biosimilars is decreasing, the authors found. Patients using Inflectra will save $1573 in OOP spending compared with how much they spent before the BBA. At the same time, OOP spending for generics is increasing.

"This is happening because branded drug manufacturers now pay a discount in the donut hole, which gets counted as out-of-pocket spending," lead author Stacie Dusetzina, PhD, associate professor of Health Policy and Ingram Associate Professor of Cancer Research at Vanderbilt University Medical Center, said in a statement. "This helps patients reach catastrophic coverage faster, where they pay 5% of the drug's price instead of 25%. Generic drug makers do not pay these same discounts, so patients have to spend more of their own money to make it to the catastrophic phase of the benefit."

The authors noted several concerns: Incentives for the use of brand-name drugs may decrease market share for generics and discourage new generic entrants; depending on plan design, patients may not be able to switch between brand-name and generic drugs to save money; and patients may have trouble switching to a brand-name drug, even if they have lower OOP costs, because of generic substitution laws.

They suggest eliminating manufacturer discounts from OOP spending calculations to reduce barriers for generic drug use or extending the discounts for brand-name drugs and biosimilars under the Part D benefit to generics as well.

"The Part D benefit needs a redesign so that it works for people needing expensive drugs," Dusetzina said. "I hope Congress will take this opportunity to make changes to Part D, including making sure that generic drug users aren't overpaying for these drugs."■

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# Rising Generic Prices Help Drive Up Cost of WHO List of Essential Medicines in US

ALLISON INSERRO

**A STUDY RELEASED** Wednesday in The BMJ looking at Medicare Part D spending on generic and brand name drugs from the list of essential medications maintained by the World Health Organization (WHO) found that spending is increasing because of pricing increases for some older, generic drugs, as well as new medications. There are now fewer

manufacturers of these generics, the study noted.

Earlier this year, a report said drug shortages and higher prices were putting US patients at risk. That report looked at spending and utilization within hospitals between 2015 and 2017.

This retrospective study drew upon a cost analysis of the Medicare Part D Prescriber Public Use File, detailing annual generic and brand name drug prescribing and spending from 2011 through 2015.

The WHO's Model List of Essential Medicines (MLEM) defines a critical set of drugs that constitute the "minimum medicine needs for a basic healthcare system." Cross referencing the MLEM with all 4498 drugs in the Medicare Part D data resulted in 319 essential medicines. The authors excluded 73 products and added 19 generic formulations of already included medicines for cases in which the brand name was prescribed more frequently than the generic.

Of the 265 essential medicines, 197 (74%) were generic. Medicare Part D spending on those drugs were $87.2 billion, with annual spending increasing from $11.9 billion in 2011 to $25.8 billion in 2015 (116%). The report said spending was driven largely by the increased use of 2 new drugs used to treat hepatitis C.

Patients' out-of-pocket (OOP) spending for essential medicines over the same period was $12.[1] billion. Total annual OOP spending increased from $2 billion to $2.9 billion (47%), and annual per beneficiary OOP spending on these drugs increased from $20.42 to $21.17 (4%).

Total prescription count increased from 376.1 million to 498.9 million (33%), and cumulative beneficiary count grew from 95.9 million to 135.8 million (42%).

The per unit cost of half of the drugs increased faster than the average inflation rate during this period. Moreover, 9 (3%) of the essential medicines saw per unit cost hikes of more than 100 times the inflation rate; 11 (4%) had per unit cost increases of between 50 and 100 times the inflation rate.

Medicines with per unit cost increases of more than 100 times the average inflation rate included the brand name drugs albendazole (Albenza), pyrimethamine (Daraprim), and penicillamine (Cuprimine) and the generic drugs tetracycline, clomipramine, mannitol, griseofulvin, chlorpromazine, and doxycycline hyclate.

OOP costs are known to be 1 of the factors affecting patient adherence to prescribed medications; policy makers should take note of changes that can help ensure that essential medicines remain accessible, the study said, lest other healthcase costs rise. For instance, legislative changes that allow CMS to negotiate drug prices or allow the importation of drugs from other countries, under specific conditions and circumstances, could help alleviate some of the pressure, the study said.■

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# Pfizer Gets FDA Approval for Tafamadis for ATTR-CM

ALLISON INSERRO

**THE FDA APPROVED** Pfizer's transthyretin stabilizer tafamidis, the first treatment for cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM), a rare, incurable disease. Pfizer will sell the oral drug in 2 dosage forms under the names Vyndaqel and Vyndamax. According to Reuters, Pfizer set the list price at $225,000 annually.

ATTR is characterized by the buildup of abnormal deposits of misfolded protein called amyloid in the heart and is defined by restrictive cardiomyopathy and progressive heart failure. The ap proval was based on data from the pivotal phase 3 Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), the first global, double-blind, randomized, placebo-controlled clinical drug study for this disease. In ATTR-ACT, tafamidis significantly reduced the hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared with placebo over a 30-month period

(*P* = .0006). Additionally, individual components of the primary analysis demonstrated a relative reduction in the risk of all-cause mortality and frequency of cardiovascular-related hospitalization of 30% (*P* = .026) and 32% (*P* <.0001), respectively, with tafamidis versus placebo. Approximately 80% of total deaths were cardiovascular-related in both treatment groups.

Tafamidis also had significant and consistent treatment effects compared with placebo on functional capacity and health status first observed at 6 months and continuing through 30 months. Specifically, tafamidis reduced the decline in performance on the 6-minute walk test (P<.0001) and reduced the decline in health status as measured by the Kansas City Cardiomyopathy Questionnaire–Overall Summary score (*P* <.0001).

Previous options included symptom management, and, in rare cases, heart (or heart and liver) transplant. It is estimated that the prevalence of ATTR-CM is approximately 100,000 people in the United States and only 1% to 2% of those patients are diagnosed.

According to the Amyloidosis Foundation, wild-type ATTR is considered a disease of aging and typically affects men; patients are being diagnosed at a younger age. In some cases, the first symptom is carpal tunnel syndrome as proteins deposit in the wrist; protein involvement may also involve the spine or tendons in the arm. The foundation said that for hereditary ATTR, there are approximately 136 different genetic variations in ATTR, and at least 60 genetic variations in non-TTR hereditary amyloidosis diseases.

The recommended dosage is either Vyndaquel 80 mg orally once daily, taken as four 20-mg capsules, or Vyndamax 61 mg orally once daily, taken as a single capsule. Pfizer said that Vyndamax was developed for patient convenience and that the 2 formulations are not substitutable on a per-milligram basis. ■

# FDA Expanding Patent Information Available to Generic Drug Manufacturers

ALLISON INSERRO

**THE FDA SAID** Tuesday it is expanding a database used by generic drug manufacturers to understand when their product can be approved and marketed. The Paragraph IV Patent Certifications List tells drugmakers about 180-day exclusivity related to generic challenges of patents on branded drug products.

Under the Hatch-Waxman amendments, a company can seek FDA approval to market a generic drug before the expiration of patents related to the branded drug. As part of that approval process, a generic applicant must provide in its application a "certification" that a patent submitted to FDA by the brand-name drug's sponsor and listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) is, in the generic drugmaker's opinion and to the best of its knowledge, invalid, unenforceable, or will not be infringed by the generic product. This certification is called a "Paragraph IV Certification."

Until now, the list included the name of the drug product, dosage and strength, and the date on which the first substantially complete generic drug application that contained a Paragraph IV Certification was submitted to the agency. The FDA said it will add the status of any 180-day exclusivity decisions for individual drug products along with other information about the dates of first approval, marketing status, and expiration dates of blocking patents.

The update may allow other applicants to understand which of their specific generic drug applications may have a higher likelihood of being approved sooner and may provide more transparency into the process. For instance, if the FDA approves an Abbreviated New Drug Application but the generic product is not available for an extended time, it may signal so-called gaming tactics to block competition.

The FDA said it will also include the number of applicants that are potentially eligible for 180-day exclusivity, which will tell other manufacturers about the possible future generic competition for a product.

In addition, the FDA said it plans to clarify how it handles situations where a final approval must be converted to tentative approval if a specific product is ordered to cease marketing due to a patent infringement ruling. Other additional guidance and policy changes to assist generic drug makers are coming, the FDA said.

Generic drugs represent the bulk of US prescriptions, and significant price decreases do not typically occur until there are at least 3 generic drugs on the market, the FDA has said.■

# Orphan Drugs Are Driving Skyrocketing Drug Costs, AHIP Finds

LAURA JOSZT

**THE PRICE OF** orphan drug medications is increasing at a far more rapid pace than that of other specialty and traditional drugs, according to a new report from America's Health Insurance Plans (AHIP).

The new study has shown that the average annual cost for orphan drugs is 25 times more expensive than traditional drugs. Orphan drugs have also been a key driver behind the sharp increase in annual drug costs at launch, which have grown from $9781 in 1998 to $106,149 in 2017.

"Most efforts to contain skyrocketing drug costs focus on price increases for drugs already on the market," according to the paper. "The laws are triggered only when a price significantly increases beyond the current price. What has received less attention is the fact that drugs are increasingly launched at higher prices."

In addition, orphan drugs are making up more of the drug approvals each year. In 1998, orphan drugs were only 10% of new approvals, but that increased 4-fold to 44% in 2017. While the share of specialty drug approvals has stayed mostly steady over the last 20 years, the share of traditional drug approvals has declined from 65% in 1998 to 20% in 2017.

The fact that orphan drugs are accounting for a larger portion of drug approvals, while traditional drugs account for a smaller portion, accounts for some of the increase in the average annual drug costs, AHIP noted in the paper.

Further exacerbating the cost issue is the fact that orphan drugs, which are supposed to target rare diseases, are sometimes used to treat more common diseases. AHIP pointed to the examples of Remicade, which was approved as an orphan drug to treat Crohn disease but has since been approved to treat common diseases like rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. There are also instances of drugs approved to treat common diseases and later approved for an orphan indication, such as Enbrel and Humira.

While the pharmaceutical industry points to small patient populations with rare conditions to justify high prices on orphan drugs, AHIP has previously found that revenues generated by orphan drugs "primarily come from their non-orphan and off-label use."

AHIP concluded the paper noting that since the target patient population for orphan drugs may not be as small as portrayed, these drugs do not have as limited of an impact on overall healthcare costs as some might think.

"Every patient deserves to get the medications they need at a cost they can afford, but drug makers are gaming well-intentioned legislation to generate outsized profits from drugs intended to treat a small population of patients with rare diseases," Matt Eyles, president and chief executive officer of AHIP, said in a statement. "Now more than ever we need lawmakers to revisit the Orphan Drug Act. We must balance the incentives to develop new treatments for rare diseases while preventing drug makers from exploiting the system with launch prices that defy gravity, blocking competition, and increasing their prices on the same products year after year." ■

# Despite More Competition, Medicare Costs for MS Drugs Rose Steadily Over 10 Years

LAURA JOSZT

**OVER THE 10-YEAR** period from 2006 to 2016, the price of self-administered disease-modifying therapies (DMTs) for multiple sclerosis (MS) rose so sharply that seniors with Medicare Part D coverage saw a 7.2-fold increase in out-of-pocket costs, according to new research published in *JAMA Neurology*.[1]

Researchers from the University of Pittsburgh assessed prices, market share, and spending on self-administered DMTs for MS (ie, glatiramer acetate, interferon β-1a, interferon β-1b, fingolimod hydrochloride, teriflunomide, dimethyl fumarate, and peginterferon β-1a). The study used claims data from 2006 to 2016 for a 5% sample of Medicare beneficiaries, which was approximately 2.8 million beneficiaries per year.

"We wanted to see how increases in list prices translated to increases in out-of-pocket spending, and we discovered that actual price increases do get passed down to patients, and that can negatively affect access," study senior author Inmaculada Hernandez, PharmD, PhD, assistant professor of pharmacy at the University of Pittsburgh, said in a statement.

Before 2009, there were only 4 self-administered DMTs to treat MS on the market in the United States, but since then 7 branded drugs entered the market. The annual cost of treatment for each agent increased at a mean rate of 12.8% annually, the authors wrote. They note that fingolimod and brand-name glatiramer, 20 mg, were consistently at the higher end of the cost range; interferon β-1b (Extavia) and generic glatiramer, 20 mg, were on the lower end during the study period.

Over the study period, spending by Medicare on these treatments increased 10.2-fold from $7794 to $79,411 per 1000 Medicare beneficiaries. Patients' out-of-pocket costs increased 7.2-fold from $372 to $2673. The authors estimated that over the 10-year period, Medicare Part D spending increased in total from $396.6 million to $4.4 billion, and out-of-pocket costs increased in total from $18.9 million to $149.4 million.

"We're not talking about patients without health insurance here," Hernandez said. "We're talking about insured patients, under Medicare. Still, they are paying much more for multiple sclerosis drugs than they were 10 years ago."

In an accompanying editorial,[2] authors from Oregon Health & Science University highlighted the "disturbing trend" that prices were increasing in parallel, and noted that the entry of new products seems to only propel costs higher.

Currently, there are 19 FDA-approved DMTs for MS, and prices continue to rise for these drugs. The authors acknowledge pharma's argument that rising costs reflect research and development costs, but they point to the continuously increasing prices of the original 3 drugs approved.

Neurologists, they wrote, should care about the rising costs and should also seek to minimize financial burdens on patients just as they would minimize physical adverse effects of treatments. The authors pointed to Mylan's generic formulation of glatiramer acetate, which dropped in price and is now the lowest-cost DMT on the market.

They encouraged neurologists to engage with pharmaceutical and biotechnology companies about unreasonable price increases and to urge law makers to pass legislation targeting these rising drug prices for MS therapies.

"Remaining silent should not be an option," the authors wrote. "The development of DMT for MS has been one of the great achievements of neurology in the past 25 years. Neurologists should not allow the unfettered increases in price for these drugs hurt the health care system or patients."

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