MAY 2018 | VOLUME 5, ISSUE 2

MRx TREND ALERT

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CONTINUOUS GLUCOSE MONITORING (CGM): THE NEXT GENERATION OF DIABETES CARE?

A world without daily fingersticks is a diabetic patient's dream! For decades, blood glucose meters (BGMs), testing strips, and fingersticks have been the cornerstone of blood sugar self-monitoring; however, BGMs are cumbersome and are not integrated devices. Although these conventional methods are not antiquated yet, CGMs are clearly making progress.

Several therapeutic CGMs have received United States (US) Food and Drug Administration (FDA) clearance, each with varied features. At their core, CGMs provide continuous 24-hour, real-time, glucose measurement and monitoring using a small sensor attached subcutaneously (SC) to the body. Results are sent wirelessly via an attached transmitter or a mobile reader to a receiver, smartphone, or insulin pump. Although the sensor requires changing every 7 to 10 days and calibration is still needed for most CGMs, two recent CGMs, the Freestyle® Libre (for adults) which uses flash technology and Dexcom G6® (for pediatrics and adults), have eliminated the need for routine user fingerstick calibration. The first fully interoperable CGM, Dexcom G6, can communicate with other medical devices and electronic interfaces, such as insulin pumps, BGMs, and smartphones. While older CGMs were approved as class III medical devices, this integrated CGM (iCGM) was authorized as a class II medical device with special controls, reducing the regulatory burden for future iCGMs that qualify for FDA's *de novo* pathway. Another system, the Guardian™ Connect System offers predictive alerts for glucose levels up to 60 minutes in advance and utilizes artificial intelligence.

For years, Medicare considered CGM systems "adjunctive," since FDA approval called for confirming blood glucose levels using a fingerstick prior to insulin dosing. Improved systems, allowing users to make dosing treatment decisions based on CGMs, led to "therapeutic" CGMs and paved the way for reimbursement under the durable medical equipment (DME) umbrella. In 2017, the Centers for Medicare and Medicaid Services (CMS) made headlines when it announced coverage of Dexcom G5®, and subsequently FreeStyle Libre, under Part B. CMS coverage criteria for a therapeutic CGM applies to certain patients with a diagnosis of type 1 or 2 diabetes who require intensive management of their insulin.

With 30.3 million adults with diabetes, CGMs provide vast opportunities, even though CGMs are not infallible. CGMs can potentially be used in a variety of diabetes diagnoses and, particularly, in those with hypoglycemic unawareness. Even non-diabetic self-enthusiasts are using CGMs to learn about glucose trends and choices, opening up the chance for CGMs to become mainstream. As CGM technology, reliability, and reimbursement evolve,

CGMs become the new standard in glucose monitoring, eliminating the need for troublesome fingersticks, facilitating treatment decisions, and further clearing the way to a bionic pancreas. ■

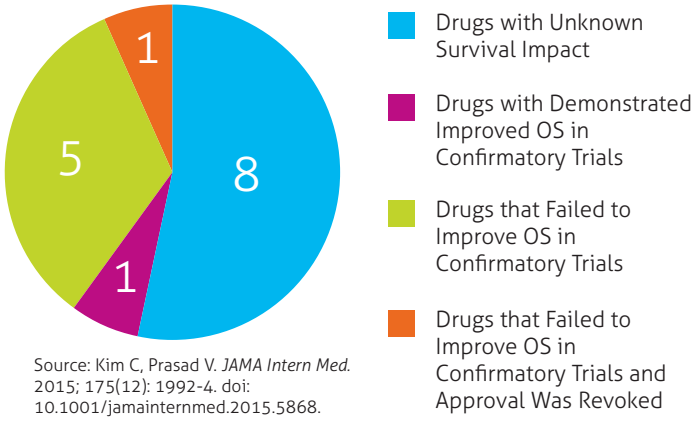
ACCELERATED APPROVAL PROGRAM: IS THE BALANCE OF SPEED AND SAFETY OUT OF EQUILIBRIUM?

In 1992, the FDA initiated the Accelerated Approval (AA) Program with a goal of speeding up the approval process for new drugs that either fill an unmet need or treat serious diseases. Much of the political push for this program came from public activism in the 1980s and early 1990s to find treatments for human immunodeficiency virus (HIV) patients. The program may consider data regarding surrogate, or indirect, endpoints rather than clinical outcomes. For instance, a cancer medication may be granted AA based on shrinkage of tumor size or duration of progression free survival (PFS) instead of overall survival (OS) improvement. If approved under AA, the sponsor is required to conduct post-marketing trials to verify the anticipated benefit. Once verified and submitted to the FDA, the FDA may grant full, or traditional, approval for the drug. If clinical trials do not confirm a benefit, the FDA may take steps to remove the drug from the market.

Approving a drug either too soon or too late can result in patient harm. In some ways, the AA program shifts the equilibrium of FDA concern to erring slightly toward the former. Based on this shift, how often does the FDA remove drugs that have not demonstrated the expected value in postmarketing trials? A study of cancer drug approvals from 2008 to 2012 found 36 drugs (67% of approvals) were based on surrogate endpoints, 15 of which received AA. In a median follow-up of 4.4 years, only 1 drug approved via AA was subsequently shown to improve OS in randomized trials, 6 failed to improve OS, and the remaining 8 had an unknown survival impact (see Figure 1). AAs are now estimated to constitute about 10% of new drug approvals (13% of novel approvals in 2017). Confirmatory trials may take years to complete, at which point, even if the drug does not demonstrate a benefit in a clinical endpoint, the sponsor may have made substantial profit in the meantime, even at the safety or cost expense of patients and payers.

As a commonly cited case study, in 2011, the FDA announced that the bevacizumab (Avastin®) indication for metastatic HER2-negative breast cancer had been withdrawn, as it was no longer considered safe and

Figure 1. Outcomes of Confirmatory Trials of Oncology AA Agents, 2008 - 2012
(number of drugs)



Source: Kim C, Prasad V. *JAMA Intern Med.* 2015; 175(12): 1992-4. doi: 10.1001/jamainternmed.2015.5868.

effective for this specific indication. Bevacizumab was approved under the AA Program in 2008 based on a study that found an increase in PFS in metastatic HER2-negative breast cancer patients. However, postmarketing studies found a higher incidence of serious adverse effects with bevacizumab and not as significant a benefit as initially thought. As a result, the FDA removed the metastatic HER2-negative breast cancer indication. In 2017, Merck received AA for pembrolizumab (Keytruda®) for select second-line cases of head and neck squamous cell carcinoma in combination with another treatment. However, in the KEYNOTE-040 trial, the drug failed to meet the OS endpoint compared to standard therapy. Nevertheless, this indication remains.

Under an ethical code in which the first rule is "do no harm," the balance of safety and speed to market is critical for patient care. For payers, interpreting the benefit of these AAs, optimizing safety, and determining their ideal role in therapy proves challenging, particularly when the price may not match the evidence. ■

CHANGING HEALTHCARE TARGETS: CLINICAL IMPACT OF PATIENT REPORTED OUTCOMES

A patient reported outcome (PRO) is a measurement of patient health that is obtained directly from the patient, without interpretation from another person (e.g., clinician). PROs of health status can be physical, mental, or social. In clinical trials, PROs may be used to determine disease severity, assess a patient for inclusion, and provide a risk-benefit evaluation, among other things. A greater emphasis has been placed on capturing PROs to better understand the patient's perceived value of care.

Recent legislation, such as the 21st Century Cures Act, aimed to improve and expand use of PROs to support a more effective and efficient drug development process. Although integrating PROs into electronic health records has increased in interest, there is limited guidance on how best to implement this information and reduce barriers to routine collection of data. Nonetheless, key studies have provided a glimpse of the clinical significance of PROs.

A recent study by Basch and colleagues assessed the clinical impact of incorporating PROs into clinical care. Enrolled patients were randomly assigned either to a usual care group (n=325) or to a PRO group (n=441). The PRO group provided a self-report of common symptoms at and between visits. If an individual reported a severe or worsening symptom, an e-mail alert was sent to a healthcare provider and resulted in a nurse performing timely direct outreach to the patient. Usual care consisted of discussing symptoms at visits, and patients could contact providers if concerned in between visits. The study demonstrated that the use of PROs resulted in improved health-related quality of life, fewer emergency room visits and hospitalizations, and longer quality-adjusted and overall survival. In addition, a systematic review of 24 controlled trials evaluating PROs found that routine use of PROs improved symptom control, increased supportive care measures, and improved patient satisfaction, despite the wide variability in design and use of PRO interventions.

In an era of increased interest in resource stewardship, patient-perceived benefit, and cost-sharing, PROs provide insight into value-based healthcare. Further, PROs may offer not only patient-centered care but also an improvement in traditional clinical outcomes. ■

MEDICAL PHARMACY CORNER

AFFORDABILITY AND ACCESS FOR INNOVATIVE DRUGS

The promise offered by novel drug therapies has never been higher. As described in a prior edition of the MRx Trend Alert, chimeric antigen receptor T-cell (CAR-T) therapies, including tisagenlecleucel (Kymriah™) and axicabtagene ciloleucel (Yescarta®), have provided hope to many patients with advanced hematologic malignancies.

The Institute for Clinical and Economic Review (ICER) recently published an evidence review of CAR-T therapies. It should be noted this review was conducted prior to tisagenlecleucel's April 2018 approval for use in certain non-Hodgkin's lymphoma (NHL) patients; instead, the ICER review focuses only on the use of tisagenlecleucel for refractory acute lymphoblastic leukemia (ALL) and axicabtagene ciloleucel for certain types of refractory NHL. ICER gave both agents a "B+" rating for their respective indications. This rating equates to a high certainty of a net health benefit compared to other currently available treatment options.

The primary aim of the ICER report on CAR-T therapies was to estimate the cost-effectiveness of these treatments. While CAR-T therapies do provide net health benefits to appropriately selected patients, prices ranges from $375,000 to $473,000 for the drug therapy alone. This figure does not include additional charges, such as hospitalization for potential management of adverse events. When combined, the overall cost of treating a patient with a CAR-T has the potential to approach a million dollars per patient. These figures alarm payers nationwide, who are struggling to comprehend how they will pay for these expensive therapies in their current business model. Reimbursement strategies, such as bundled payments, outcomes-based contracting, and even annuity payments, have all been discussed.

The ICER report determined that both tisagenlecleucel for refractory ALL and axicabtagene ciloleucel for certain refractory NHLs met the commonly cited cost-effectiveness threshold ($150,000 per Quality-Adjusted Life Year [QALY]) in most of the scenarios tested. ICER further determined that every eligible ALL patient in the US could be treated with tisagenlecleucel, but only 38% of eligible NHL patients could be treated with axicabtagene ciloleucel annually before the costs would exceed an overall budget impact threshold of $915 million annually. This threshold was chosen based on the overall growth of the US economy. Therefore, ICER issued an "affordability and access alert" for axicabtagene ciloleucel, which warns of the possible need for funds to be diverted away from other healthcare services to pay for this therapy. Otherwise, the resulting necessary rise in healthcare insurance premiums may threaten overall access to healthcare for many individuals.

ICER put forth several key policy recommendations aimed at ensuring sustainable access to CAR-T therapies for those needing them, including patient education, early (pre-FDA approval) dialogue amongst stakeholders, limiting care to centers of excellence, long-term registry follow-up of treated patients, and, finally, the need for innovative payment models. ■

PIPELINE REPORT: 2ND AND 3RD QUARTER 2018

DRUG MANUFACTURER	CLINICAL USE	ANTICIPATED DATE	PROJECTED MARKET IMPACT
Select Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
pegvaliase Biomarin	Phenylketonuria	May 25, 2018	SC PEGylated recombinant phenylalanine ammonia lyase enzyme; provides enzyme replacement therapy for severe phenylketonuria in adults; Orphan drug; Priority review
baricitinib Eli Lilly	Rheumatoid arthritis	June 2018	Oral Janus kinase inhibitor; will compete with Pfizer's Xeljanz® and Xeljanz XR
cannabidiol (Epidiolex®) GW/ Otsuka	Dravet syndrome; Lennox-Gastaut syndrome	June 27, 2018	Oral purified extract of plant-derived cannabinoid, a non-psychoactive molecule from the cannabis plant; Fast track; Orphan drug; Priority review; Rare pediatric disease product
binimetinib Array	Melanoma	June 29, 2018	Oral mitogen-activated extracellular kinase (MEK) inhibitor for BRAF-positive, advanced, unresectable/ metastatic melanoma; Orphan drug
encorafenib Array	Melanoma	June 29, 2018	Oral BRAF inhibitor for BRAF-positive, advanced, unresectable/ metastatic melanoma; Orphan drug
migalastat (Galafold™) Amicus/ GlaxoSmithKline	Fabry disease	August 13, 2018	Oral chaperone therapy that restores α-GAL A enzyme activity; reduces build-up of globotriaosylceramide; first-in-class; Fast track; Orphan drug; Priority review
Select New Generics/ Patent Expirations			
fentanyl citrate generic for Orexo's Abstral®	Pain	June 2018	Settlement agreement with Actavis/ Teva; US sales of $17 million in 2016
treprostinil generic for United Therapeutics' Remodulin®	Pulmonary arterial hypertension (PAH)	June 26, 2018	Settlement agreement with Sandoz; US sales of $602 million in 2016
benzoyl peroxide/ clindamycin phosphate generic for Valeant's Acanya®	Acne	July 1, 2018	Settlement agreement with Actavis/ Teva; appears eligible for 180-day exclusivity; US sales of $74 million in 2016
Select Biosimilars/ Follow-on Products			
ABP980 – biosimilar to Genentech's Herceptin® Amgen	Breast or gastric/ gastroesophageal cancer (HER2-positive)	May 28, 2018	IV HER2/neu receptor antagonist; product launch may be delayed due to regulatory hurdles; Herceptin had US sales of $2.73 billion in 2016
Myl-1401H – biosimilar to Amgen's Neulasta® Mylan/ Biocon	Neutropenia associated with chemotherapy; Neutropenia associated with radiation	June 4, 2018	SC colony stimulating factor; product launch may be delayed due to regulatory hurdles; Neulasta had $4.16 billion in US sales in 2016
Basalog® – follow-on to Sanofi's Lantus® Mylan/ Biocon	Type 1 diabetes mellitus; Type 2 diabetes mellitus	July 2018	SC long-acting insulin; new drug application (NDA) submitted via 505(b)(2) pathway; Lantus had $8.99 billion in US sales in 2016