Alaska Pharmacists Association

Continuing Education Home Study Series

Program 0139-0000-21-202-H04-P/T
Quarterly AKPhA Newsletter
Release Date 5/24/2021
Expiration Date 5/24/2024
CPE Hours: 2.0 (0.2 CEU)

This lesson is a knowledge-based CPE activity and is targeted to pharmacists and technicians in all practice settings.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. State two positive changes you can make to your practice following participation in this series.
2. Summarize three practice updates or changes you acquired while participating in this series.

Disclosure

The author(s) and other individuals responsible for planning AKPhA continuing pharmacy education activities have no relevant financial relationships to disclose.

Fees

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Biologics, Biosimilars and Interchangeability

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The topic of biological agent interchangeability and acquiring that designation is one of current debate. Since biologics are big, complex, and uniquely derived from living cells, a biosimilar can never be exact to it. The relationship of biologics and biosimilars cannot be compared to the relationship between brand and generic due to these reasons. Non-biological drugs are small molecules and can be replicated exactly and, therefore, interchanged or substituted without the same concern.[1] Since there are no current biologics and biosimilars designated as interchangeable, knowing how they are named and differentiated is important to avoid mistakes.[2]

Naming and Recognition of Biological Agents

The first biologic drugs on the market only consisted of a core name (e.g. trastuzumab), designated by the United States Adopted Names for Drugs Council. A suffix consisting of random letters was introduced to help distinguish biologic, biosimilars and interchangeable agents from each other (e.g. trastuzumab-anns, trastuzumab-dkst, trastuzumab-dttb, trastuzumab-pkrb, trastuzumab-qyyp).[3] In 2017 the Food and Drug Administration (FDA) considered retroactively assigning suffixes to reference biologic products already on the market, concerned that a suffix could cause a perception of inferiority but decided against it to avoid negative repercussions.[4] Since then, all new biologic and biosimilar drugs consist of a core name and suffix. This naming schematic will allow biological products to be grouped together in electronic databases to allow health care providers to be able to locate and identify core name grouped agents more easily.[4]

A biosimilar is designated as such when it displays no meaningful clinical differences in safety, purity, and potency to its reference biologic. Biosimilars may be approved for a reference biologic indication without direct studies in that indication as long as total evidence in application supports a demonstration of biosimilarity

for at least one of the reference product's indications. This is termed as "extrapolation" and is a key component of the abbreviated pathway. The basis of extrapolation includes "(1) all available data and information in the biosimilar application, (2) FDA's previous finding of safety and efficacy for other approved indications for the reference product, and (3) knowledge and consideration of various scientific factors for each indication."[5] It is important to note that the biosimilar manufacturer must supply enough supportive data to scientifically justify extrapolation.

Interchangeability between Biological Agents

Biologics play a major role in the treatment of cancer and serious illness. Utilization has increased more than twice the rate of other drugs since 2018. While biologics only make up approximately 2% of all US prescriptions, they account for more than a third of net drug spending.[6] The development and use of biosimilars improves access of treatment to patients. Often cancer patients discontinue or skip treatment due to high out-of-pocket costs.[7] A potential savings from biosimilar use in treatment over its biologic originator is estimated at $24-$150 billion over 2017-2026.[6]

In 2010, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) which abbreviated the approval pathway for biosimilars to create competition and drive costs down. In May 2019, the FDA published guidance on interchangeability requirements.[8]

According to the BPCIA, the process of interchangeability requires that "an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as a reference product in any given patient."[4] Additionally, they must demonstrate that there is no change in safety risk or diminished efficacy switching or alternating with the reference product as compared without the switch or alternation.

The FDA recommends two study designs to establish interchangeability. The first approach is "a dedicated switching study" which begins with all patients starting on the reference product, then branching into two arms: a control arm of the reference biologic and an intervention arm alternating between the biosimilar and reference biologic. [9]

The second approach is "the integrated study" which is broken into a biosimilarity study portion and a switching study portion. During the biosimilarity study portion, the biosimilar and reference biologic go head-to-head for a designated time. Then, during the switching study portion, patients in the reference biologic arm are re-randomized and assigned into a designated switching study like the first approach.[9]

Interchangeable status would allow pharmacists to substitute a biosimilar for its reference biologic according to current Alaska Pharmacy Statutes and Regulations with proper prescriber and patient communication/documentation.[10] Pharmacists may also have a leading role in the introduction of biosimilars into healthcare systems. Having a firm understanding of the pharmacology, development, regulations and guidelines places the pharmacist as a crucial resource. Taking on this role will help patients and healthcare teams to make informed decisions on therapy choice and formulary inclusion.[11] Increased access through more affordable biosimilars may treat an additional 1.2 million patients over the next 10 years, with the most impact on women, lower-income, and older patients.[12] It is exciting to see the future of medicine and potential impact pharmacy has in it.

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2020 AHA CPR/ECC Guidelines Update

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Cardiac arrest is a leading cause of mortality and morbidity in the United States.[1] The American Heart Association for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) provided the most recent update in October 2020. Updated guidelines are necessary for healthcare professionals to stay current on changes occurring within clinical practice. For guidance in treatment courses, AHA updated recommendations, algorithms, and visual aids for adults and pediatric patients. New algorithms and diagrams include opioid associated emergencies, cardiac arrest in pregnancy, post-cardiac arrest care, neuroprognostication guidance, chain of survival, and tachycardia/bradycardia management in pediatric patients.

The adult basic and advanced life support guidelines implemented intravenous access over intraosseous access in fluid and medication administration. In addition, it confirmed that double sequential defibrillation is not recommended in advanced cardiac life support.[2] Recommendations and rationales are listed in Table 1. A post-cardiac arrest care algorithm was created for stabilized patients to guide maintenance of blood pressures, monitoring for seizures, neuroprognostication, and targeted temperature management. [3]

The pediatric basic and advanced life support recommendations updated the ventilation rate to 1 breath every 2-3 seconds (20-30 breaths per minute), the use of cuffed endotracheal tubes versus uncuffed, administration of epinephrine within 5 minutes, and recommended against cricoid pressure during intubation.[4] These recommendations and rationales can be found in Table 2. The updated pediatric algorithms for management of bradycardia and tachycardia exclude the wording "poor perfusion," allowing it to be used on all bradycardic and tachycardic pediatric patients.

Opioid abuse has led to an increased number of cardiac arrests. AHA created two new algorithms for out of hospital cardiac arrest scenarios with suspected opioid overdose, one for lay-rescuers and one for healthcare professionals. The focus remains on activating an emergency response and performing high-quality CPR. Despite naloxone administration being a priority in suspected opioid overdose, CPR should not be delayed.[5]

Treating pregnant patients may come with some risks to the fetus, this is always a consideration when discussing treatment options. AHA provided an algorithm to guide cardiac arrest in pregnancy. Best outcomes for mother and baby are obtained with maternal resuscitation. This algorithm focuses on high-quality CPR with manual uterine displacement, preparation of perimortem cesarean delivery (PMCD), and maternal resuscitation. PMCD should be considered after 5 minutes if outcomes would improve the chances for the mother and baby.[6]

Recovering from cardiac arrest can be a challenging process. The AHA Chain of Survival has included an additional chain, "Recovery". This was integrated into both adult and pediatric chain of survival diagrams. Patients should be assessed for rehabilitation factors while in the hospital so that proper multidisciplinary discharge planning is optimized. Follow up for at least a year is a recommendation. This helps with transitioning care to outpatient.[7]

As part of a response team, a pharmacist can attribute to patient care and outcomes by providing drug recommendations, preparing medications, and calculating drug doses during a stressful situation. Pharmacists have become a common team member for code and rapid response situations in the hospital setting. It's important to stay current on the new guidelines to provide patients with quick and appropriate care to improve outcomes.

Table 1: Adult Basic and Advanced Life Support[2]	
Recommendations	Rationale
New: The use of double sequential defibrillation in cardiac arrest is not supported for patients unresponsive to defibrillation.	There is no current data on the usefulness of double sequential defibrillation.
New: Intravenous (IV) access should be attempted before intraosseous (IO) access.	Recently there have been some studies of poor drug efficacy with IO administration. IO access has become a popular method in cardiac arrest patients. IV access should be attempted first and is the preferred route for drug administration.
Reaffirmed: Early administration of epinephrine in nonshockable rhythms. **Reaffirmed:** Epinephrine administration after defibrillation attempts in shockable rhythms.	Early administration of epinephrine increases ROSC and survival.

Table 2: Pediatric Basic and Advanced Life Support[4]	
Recommendations	Rationale
Update for infants and children with a pulse and inadequate breathing, administering rescue breaths 1 breath every 2-3 seconds is recommended. Update for infants and children with an **advanced airway**. 1 breath every 2 to 3 seconds are recommended.	Old recommendations - Rescue breaths previously stated 1 breath every 3-5 seconds. - Advanced airway previously stated 1 breath every 6 seconds. Higher oxygenation levels showed increased rates of survival and ROSC in pediatric patients with advanced airways. There is currently no data to prove this in rescue breathing scenarios, this was chosen for standardization.
Cuffed endotracheal tubes are preferred for intubation in pediatric patients.	Some studies have shown that cuffed ETTs reduced the amount of tube changes or replacements.
Cricoid pressure during intubation is not recommended.	Studies have less successful attempts during intubation with this technique.
All pediatric patients in cardiac arrest should receive epinephrine within 5 minutes or as soon as possible once compressions have started.	The goal is to increase survival-to-discharge with cerebral and coronary perfusion.

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Gout: An Opportunity for Pharmacists

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Gout is one of the oldest recognized diseases. It was first identified by Egyptians in 2640 BC and was later recognized by Hippocrates who referred to it as the "unwalkable disease". Despite early historical clinical recognition, gout is a growing problem in developed countries. It is estimated that it affects 9.2 million adults in the U.S.[1] and accounts for approximately 7 million ambulatory visits annually at a cost of nearly a billion dollars.[2] Studies in several developed countries suggest that hospitalizations for gout are on the rise even as hospitalizations for another inflammatory arthritis (rheumatoid arthritis) are decreasing.[3,4] A single center study in 2014 suggested that as many as 70% of hospital visits for gout flares in patients with previously diagnosed gout were preventable.[5]

Gout is the most common inflammatory form of arthritis. Hyperuricemia, high concentrations of serum uric acid, can lead to the formation of monosodium urate (MSU) crystals in joints, often the big toe. MSU crystals precipitate severe inflammation and a severe sudden onset of pain. The detection of MSU crystals in the affected joint is typically required to definitively diagnose gout. Hyperuricemia is defined as any level greater than or equal to 6.8 mg/dL by the 2020 American College of Rheumatology (ACR) guidelines for the treatment of gout.[1] It is important to note that the incidence of acute gout in patients with urate levels greater than 9mg/dL is as low as 5% per year.[6] Hyperuricemia is a risk factor for developing gout but is not diagnostic for gout.

Uric acid is a product of purine catabolism and almost all excess uric acid is excreted through the glomeruli in the kidneys. Cell turnover and diet are the main sources of purines in the body. A diet rich in meat, fructose, and alcohol (especially beer) can lead to higher levels of uric acid in the blood; however, most cases of hyperuricemia are caused by urate under excretion in the kidneys.[7] In addition to dietary sources of excess purines, proliferative disorders and cytotoxic drugs can lead to an over production of uric acid. Hypertension, chronic kidney disease, diuretic use, dehydration, and other endocrine disorders can lead to under-excretion of uric acid.

There are four stages of gout.

1. Hyperuricemia – can precipitate gout
2. Acute flares – characterized by pain and joint inflammation
3. Intercritical periods – no symptoms but crystals still depositing
4. Advanced gout – characterized by frequent pain, joint destruction, kidney damage, and cardiovascular complications[7]

The goals of pharmacologic therapy are to manage the symptoms of acute and chronic gout and to prevent recurrent episodes and long-term complications. In acute flares, patients are treated first line with high dose NSAIDs, steroids, or colchicine depending on patient specific features. If patients have had more than two flares in a 12-month period, urate-lowering therapy (ULT) is recommended by both the American College of Rheumatology (ACR) and the American College of Physicians (ACP).[1,8] There are two primary strategies for urate lowering therapy. Xanthine oxidase inhibitors (XOI) are considered first line and block the creation of uric acid by inhibiting an enzyme that produces it in the body. The XOI allopurinol is the first line treatment for ULT.[1] The second primary ULT strategy is to increase the excretion of uric acid with a uricosuric drug. Ninety percent of uric acid that is filtered in the kidneys is reabsorbed and the medication probenecid effectively targets transport proteins in the proximal renal tubules. For refractory gout or to prevent gout precipitated by tumor lysis syndrome, uricases can be used to breakdown gout into allantoin. The kidneys more readily excrete allantoin. Pegloticase is the only FDA approved uricase. It is effective but considered last line because it is expensive and requires infusions by a rheumatologist every 2 weeks.

The ACR 2020 guidelines recommend a treat to target strategy when initiating ULT. Both the ACR and ACP recommend low-dose colchicine or scheduled NSAIDs for flare prophylaxis during the first 3 – 6 months of ULT because there is an increased risk of flares when ULT is initiated. Urate lowering therapy is NOT initiated during an acute flare; however, if a patient is already on an ULT medication they should continue to take the medication while treating the acute flare.[1] ULT is initiated > 2 weeks after symptoms of an acute flare are gone. For allopurinol, the starting dose is typically 100 mg – 300 mg/day. The treat to target strategy involves dose titration of allopurinol based on serial urate levels taken every 2 – 5 weeks until serum urate levels are below 6 mg/dL. If target levels cannot be

reached with the max (800 mg/day), tolerated doses of allopurinol second line agents can be added as needed. Once the target level is reached, uric acid levels should be monitored every 6 – 12 months. [1]

There are two FDA approved XOIs in the United States, allopurinol and febuxostat. Allopurinol is considered first line because it is considerably cheaper than febuxostat and febuxostat has a black box warning. [1] Patients with established cardiovascular disease have a higher rate of CV death when treated with febuxostat compared to allopurinol.[9] Allopurinol is not without risks. African Americans and patients of Southeast Asian descent should be screened for the HLA-B*5801 gene variant because it carries an increased risk of a Stevens-Johnson syndrome type reaction.[1] Probenecid is the only FDA approved uricosuric available in the United States. It can be used as monotherapy or in combination with a XOI. [1] It should not be used in patients with a history of nephrolithiasis, renal impairment (CrCL < 50mL/min or eGFR < 30mL/min), or in conjunction with NSAIDs.

Studies in the past decade have shown the potential for pharmacist led interventions to improve ULT adherence, as well as the number of patients reaching their urate goals.[10,11] Community pharmacists and clinic based pharmacists can help encourage providers to titrate ULT effectively and then remain adherent to their regimens. Medication adherence and ineffective ULT titration are a key driver of preventable ambulatory and emergency room visits due to gout complications.

Key opportunities for pharmacist intervention:

- Acute flare prophylaxis at ULT initiation?
- ULT titrated to < 6 mg/dL?
- Medication choice appropriate based on patient specific factors?
    - Allopurinol – Renal dosing/HLA-B*5801 testing for African Americans/Southeast Asian descent
    - Febuxostat – Inappropriate if known cardiovascular disease
    - Probenecid – Renal dosing/NSAID use/history of nephrolithiasis
    - Colchicine – Age/polypharmacy (multiple drug-drug interactions)/CKD

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Bamlanivimab and Etesevimab for Coronavirus Disease 2019

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Coronavirus Disease 2019 (COVID-19) has been at the forefront of the world for well over a year now. As of April 6, 2021, the United States Centers for Disease Control reported a total of 30,596,830 cases of COVID-19 and 554,420 deaths.[1] Multiple treatments for COVID-19 have been issued an Emergency Use Authorization (EUA) by the United States Food and Drug Administration (FDA). One of the more recent treatments issued an EUA on February 9, 2021 was bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients ($\geq$12 years old and $\geq$ 40 kg) with positive results for direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19 and/or hospitalization.[2, 3] Bamlanivimab monotherapy was issued an EUA on November 9, 2020 for the treatment of mild to moderate COVID-19.[2] Understanding the differences between bamlanivimab monotherapy and bamlanivimab and etesevimab administered together is important.

Data Supporting Combination Therapy
Bamlanivimab and etesevimab are recombinant neutralizing human IgG1 monoclonal antibodies directed against the spike protein of SARS-CoV-2 and bind to different but overlapping epitopes in the receptor binding domain of the S-protein.[4, 5] Using the combination of bamlanivimab and etesevimab together is expected to reduce the risk of viral resistance.[4] There has been a sustained increase in SARS-CoV-2 viral variants in the United States that are resistant to bamlanivimab administered alone.[6] Due to the increase in viral variants and resistance, the United States Government, in coordination with Eli Lilly and Company, stopped the distribution of bamlanivimab alone on March 24, 2021.[6]

The data from phase 2 and 3 of the BLAZE-1 trial showed lower hospitalization rates for bamlanivimab and etesevimab administered together.[4, 7] In phase 2, the proportion of subjects with COVID-19–related hospitalizations or emergency department visits at day 29 was 1% in the 700 mg bamlanivimab monotherapy group, 1.9% in the 2800mg bamlanivimab monotherapy group, 2% in the 7000 mg bamlanivimab monotherapy group, 0.9% in the combination therapy group, and 5.8% in the placebo group.[7] The only treatment group that was statistically significant was the combination group with a p-value of 0.049.[7]

In phase 3 of the BLAZE-1 trial, subjects were treated with a combination of bamlanivimab 2800 mg and etesevimab 2800 mg or placebo.[4] The primary endpoint for this trial was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29.[4] Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%), with a statistically significant p-value of less than 0.001.[4]

The data from the ongoing phase 2 BLAZE-4 trial determined the appropriate dosing to be used for bamlanivimab and etesevimab.[4] Participants in this trial were treated with a bamlanivimab 700 mg and etesevimab 1400 mg, bamlanivimab 2800 mg and etesevimab 2800 mg, or placebo.[4] The primary endpoint was the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on day 7.[4] The rates for participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 were 31% (42/135) for placebo, 14% (21/147, p-value <0.001 versus placebo) for bamlanivimab 700 mg and etesevimab 1,400 mg together, and 10% (10/99, p-value <0.001 versus placebo) for bamlanivimab 2,800 mg and etesevimab 2,800 mg together.[4] Based on the results from the trial so far, the dose of 700 mg bamlanivimab and 1400 mg etesevimab has a similar clinical effect to 2800 mg bamlanivimab and 2800 mg etesevimab.[4]

Dosing and Administration
The authorized dose is 700 mg bamlanivimab and 1400 mg etesevimab administered together as a single IV infusion as soon as possible after a positive test for SARS-CoV-2 and within 10 days of symptom onset.[4] It is important to note that bamlanivimab and etesevimab are available as solutions in separate vials and must be diluted and combined prior to administration to patients.[8] The maximum infusion rate is 310 mL/hour with an infusion time ranging from 21 minutes to 70 minutes depending on the size of 0.9% sodium chloride infusion bag and if the patient weighs 50 kilograms or more.[3] The infusion time and administration differ from administration of bamlanivimab as monotherapy. Patients must be monitored clinically during administration and observed for at least one hour after the infusion is complete.[4] Bamlanivimab and etesevimab are not authorized for use in patients who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy.[4]

Role in COVID-19
The combination of bamlanivimab and etesevimab is an option for patients with mild to moderate COVID-19. Because the drug is currently free under the EUA, cost is not a factor at this time. Pharmacists can play a role in determining patient eligibility for the administration of bamlanivimab and etesevimab. Having more treatment options for COVID-19 is a promising step to the end of the pandemic.

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COVID-19 Vaccine Overview and Updates

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Background: There are three main types of COVID-19 vaccines available or undergoing evaluation for approval in the United States.[1] Each of these vaccines have unique mechanisms of action, discussed in the table below:

- Messenger ribonucleic acid (mRNA):
  - Modified mRNA is formulated in lipid particles that enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 spike (S) antigen that is intended to elicit an immune response[2]
    - The mRNA remains in the cell cytoplasm and does not enter into the nucleus; mRNA vaccines do not interact with or integrate into the recipient's DNA[2,3]
- Viral vector:
  - The adenovirus in the vaccine is a recombinant, replication-incompetent virus vector that expresses the SARS-CoV-2 spike (S) antigen without virus propagation to elicit an immune response to the S antigen[4]
    - Replication-incompetent vector vaccines use a different vector virus that has been engineered to not replicate in vivo and to express the viral protein that is the intended immune target[3,4]
- Recombinant protein:
  - Recombinant protein vaccines are composed of viral proteins that have been expressed in one of various systems, including insect and mammalian cells, yeast cells, and plant[3]
    - Protein subunit vaccines do not require replication of the live virus, which facilitates production, although production yields depend on the ability to express the spike protein, which is variable[3]

Vaccines Currently Available in the United States: Currently, three vaccines are authorized and recommended for use in the United States to prevent COVID-19, including those manufactured by Pfizer-BioNTech, Moderna, and Janssen/Johnson & Johnson. The CDC does not recommend one vaccination over another, as all three have been proven to be effective to reduce the risk of severe illness.[1] The choice for vaccine should be based on availability.[3] It is important to note that on April 13, 2021 the Janssen (Johnson & Johnson) COVID-19 vaccine has been put on temporary hold in the United States by the CDC and FDA due to concerns of safety and implications in rare blood clot development.[5] Additionally, the AstraZeneca COVID-19 vaccine has not been approved for emergency use in the United States, but has been temporarily halted in other countries around the world due to similar concerns of safety and unacceptable risk.[6] The World Health Organization (WHO) and European Medicines Agency (EMA) have both recently stated that AstraZeneca benefits outweigh the risk of unfavorable outcomes based on an assessment of the latest data.[7] For healthcare systems and providers, it is of upmost importance to remain vigilant in staying up-to-date with the most current COVID-19 vaccination recommendations based on continuously evolving data.

Candidate Vaccines: As of April 9, 2021 the number of candidate vaccines in clinical and pre-clinical development were 87 and 186, respectively.[9]

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Characteristics of Select COVID-19 Vaccines[3,8] (data adapted from WHO and CDC)

Manufacturer (Vaccine Name)	Design	Doses and Interval	Efficacy against Symptomatic COVID-19	Storage Requirements	Important Considerations
Pfizer-BioNTech (BNT162b2)	mRNA	2 doses, 3 weeks apart	95%	Ultracold freezer (–80 to –60°C) then freezer (–25 to –15°C) for up to 2 weeks cumulative time then refrigerated (2 to 8°C) for up to 5 days	Approved in the United States
Moderna (mRNA-1273)	mRNA	2 doses, 4 weeks apart	94%	Freezer (–25 to –15°C) then refrigerated (2 to 8°C) for up to 30 days	Approved in the United States
Janssen/Johnson & Johnson (Ad26.COV2.S)	Replication incompetent adenovirus vector	1 dose	66%	Refrigerated (2 to 8°C)	Approved in the United States but placed on hold as of April 13, 2021
AstraZeneca (ChAdOx1 nCoV-19/AZD1222)	Replication incompetent adenovirus vaccines	2 doses, 4-12 weeks apart	70%	Refrigerated (2 to 8°C)	Not approved in the United States, suspended in multiple countries
Novavax (NVX-CoV2373)	Recombinant protein	2 doses, 3 weeks apart	89%	Refrigerated (2 to 8°C)	Not approved (expected FDA approval for use in the United States in May)

Program 0139-0000-21-202-H04-P/T
Quarterly AKPhA Newsletter
Release Date 5/24/2021
Expiration Date 5/24/2024
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