BioNTech COVID-19 vaccine
Administration of Dose 2 following an adverse reaction After Dose 1

The vaccine is not registered in Israel but was approved for use under Regulation 29(a) of the Pharmacists' Regulations (Preparations) 1986.

The use of COVID-19 mRNA Vaccine BNT162b2 should be in accordance with official MoH guidance which are available in the following link:

Israel Ministry of Health: "Coronavirus (COVID-19) vaccines" National Immunization Guidelines, Epidemiology Department., December 2020.
Please see the Emergency Use Authorization (EUA) Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) including Full EUA Prescribing Information on important treatment considerations for the Pfizer-BioNTech COVID-19 Vaccine via the following link: https://www.pfizermedicalinformation.com/en-us/pfizer-biontech-covid-19-vaccine. In the event this link does not work, please access the product's approved Fact Sheet, including Prescribing Information, at www.pfizer.com. Note: select fact sheet or prescribing information is excerpted further in the document.

Select Emergency Use Authorization Prescribing Information

Dosage and Administration

Vaccination Schedule for Individuals 16 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

There are no data available on the interchangeability of the Pfizer-BioNTech COVID-19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer-BioNTech COVID-19 Vaccine should receive a second dose of Pfizer-BioNTech COVID-19 Vaccine to complete the vaccination series. [1]

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine.[1]

Description

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2. [1]

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]- N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose. [1]

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.[1]

Overall safety summary

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. [1]

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%). [1]

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.[1]

Clinical trials Experience

Local and Systemic Adverse Reactions Solicited in the Study 2

For the frequency and severity of solicited local and systemic reactions, within 7 days following each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo in the subset of participants 18 to 55 years of age included in the EUA safety population who were monitored for reactogenicity with an electronic diary please refer to Table 1 and 2 from the EUA Prescribing Information. [1]

For the frequency and severity of reported solicited local and systemic reactions, within 7 days of each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo for participants 56 years of age and older please refer to Table 3 and 4 from the EUA Prescribing Information. [1]

Across both age groups, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group. [1]

Solicited reactogenicity data in 16 and 17 year-old participants are limited.[1]

For further information regarding the authorized use under the Emergency Use Authorization (EUA), please refer to the Fact Sheet for Vaccination Providers Administering Vaccine or EUA Prescribing Information for the Pfizer-BioNTech COVID-19 Vaccine.

CLINICAL DATA

Phase 1/2/3 Clinical Study

The safety, tolerability, immunogenicity, and efficacy of the vaccine candidates against COVID-19 were evaluated in an ongoing multicenter, multinational, randomized, placebo-controlled, observer-blind, phase 1/2/3 study (*ClinicalTrials.gov Identifier: NCT04368728*).[2,3]

In this study, the candidate selected for evaluation in Phase 2/3 is BNT162b2 at a 30-µg dose level in a 2 dose regimen (separated by 21 days).[2,3]

During this clinical trial, the possible reasons for definitive discontinuation of study intervention include the following: adverse events; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria or meeting 1 or more exclusion criteria).

In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it was preferred that the second dose be administered.[3]

For more details on the clinical trial, including inclusion/exclusion criteria, you can refer to the full Protocol here.

RECOMMENDATIONS

Advisory Committee on Immunization Practices (ACIP)

In the United States, the CDC's Advisory Committee on Immunization Practices (ACIP) provides recommendations regarding the routine administration of vaccines to children and adults.
For more information on ACIP, you can refer to their website at:
http://www.cdc.gov/vaccines/acip/index.html

INTERIM CLINICAL CONSIDERATIONS FOR USE of mRNA COVID-19 Vaccines Currently Authorized in the United States

The ACIP has released interim clinical considerations for the use of Pfizer-BioNTechCOVID-19 Vaccine. This information can be accessed at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html[4]

Patient counseling

Vaccine efficacy

"Preliminary data suggest high vaccine efficacy in preventing COVID-19 following receipt of two doses of mRNA COVID-19 vaccine (Pfizer-BioNTech: 95.0% [95% CI: 90.3%, 97.6%]; Moderna: 94.1% [95% CI: 89.3%, 96.8%]). Limited data are currently available regarding the efficacy of a single dose. Patients should be counseled on the importance of completing the two-dose series (of the same vaccine product) to optimize protection."

Reactogenicity

"Before vaccination, providers should counsel mRNA COVID-19 vaccine recipients about expected local (e.g., pain, swelling, erythema at the injection site, localized axillary lymphadenopathy on the same side as the vaccinated arm) and systemic (e.g., fever, fatigue, headache, chills, myalgia, arthralgia) post-vaccination symptoms. Depending on vaccine product (Pfizer vs. Moderna), age group, and vaccine dose, approximately 80–89% of vaccinated persons develop at least one local symptom and 55–83% develop at least one systemic symptom following vaccination.

Most systemic post-vaccination symptoms are mild to moderate in severity, occur within the first three days of vaccination, and resolve within 1–3 days of onset. These symptoms are more frequent and severe following the second dose and among younger persons compared to older persons (i.e., >55 or ≥65 years [for Pfizer-BioNTech or Moderna vaccines, respectively]). ***Unless persons develop a contraindication to vaccination (see below), they should be encouraged to complete the series even if they develop local or systemic symptoms following the first dose to optimize protection against COVID-19****.*

In clinical trials, hypersensitivity-related adverse events were observed in 0.63% of participants who received the Pfizer-BioNTech and 1.5% of participants who received the Moderna COVID-19 vaccine, compared to 0.51% and 1.1%, respectively, in the placebo groups. Anaphylaxis following vaccination was not observed in the Pfizer-BioNTech or Moderna COVID-19 vaccine clinical trials. However, anaphylactic reactions have been reported following receipt of mRNA vaccines outside of clinical trials.

Antipyretic or analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs) may be taken for the treatment of post-vaccination local or systemic symptoms, if medically appropriate. However, routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, as information on the impact of such use on mRNA COVID-19 vaccine-induced antibody responses is not available at this time. […]"

Contraindications and precautions

"While rare, anaphylactic reactions have been reported following vaccination with mRNA COVID-19 vaccines. Although investigations are ongoing, persons with a history of an immediate allergic reaction (of any severity) to an mRNA COVID-19 vaccine or any of its components might be at greater risk for anaphylaxis upon re-exposure to either of the currently authorized mRNA COVID-19 vaccines. For the purposes of this guidance, an immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms such as urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.

Recommendations for contraindications and precautions are described below and summarized in Appendix A. The following recommendations may change as further information becomes available.

Contraindications

CDC considers a history of the following to be a contraindication to vaccination with both the Pfizer-BioNTech and Moderna COVID-19 vaccines:

- *Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components*
- *Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])**
- *Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)**

** These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available). See Appendix B for more information on ingredients included in mRNA COVID-19 vaccines.*

Persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines. Providers should attempt to determine whether reactions reported following vaccination are consistent with immediate allergic reactions versus other types of reactions commonly observed following vaccination, such as a vasovagal reaction or post-vaccination side effects (which are not contraindications to receiving the second vaccine dose) (Appendix C).

Healthcare personnel or health departments in the United States can request a consultation from the Clinical Immunization Safety Assessment COVIDvax project for a complex COVID-19 vaccine safety question about an individual patient residing in the United States not readily addressed by CDC guidance.

Precautions

CDC considers a history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies not related to a component of mRNA COVID-19 vaccines or polysorbate) as a precaution but not a contraindication to vaccination for both the Pfizer-BioNTech and Moderna COVID-19 vaccines. These persons should be counseled about the unknown risks of developing a severe allergic reaction and balance these risks against the benefits of

vaccination. Deferral of vaccination and/or consultation with an allergist-immunologist may be considered until further information on the risk of anaphylaxis is available. The following considerations can be used to help the provider conduct a risk assessment for mRNA COVID-19 vaccination in these individuals:

- *Risk of exposure to SARS-CoV-2 (e.g., because of residence in a congregate setting such as a long-term care facility, occupation)*
- *Risk of severe disease or death due to COVID-19 (e.g., because of age, underlying medical conditions)*
- *Whether the patient has previously been infected with SARS-CoV-2 and, if so, how long ago*
    - *Note: Vaccination is recommended for persons with a history of COVID-19; however, because reinfection is uncommon in the 90 days following infection, persons with a precaution to vaccination and recent COVID-19 may choose to defer vaccination until further information is known about the risk of anaphylaxis following vaccination.*
- *The unknown risk of anaphylaxis (including fatal anaphylaxis) following mRNA COVID-19 vaccination in a person with a history of an immediate allergic reaction to other vaccines or injectable therapies*
- *Ability of the patient to be vaccinated in a setting where appropriate medical care is immediately available for anaphylaxis*

Neither contraindications nor precautions to vaccination

Allergic reactions (including severe allergic reactions) not related to vaccines, injectable therapies, components of mRNA COVID-19 vaccines (including PEG), or polysorbates, such as food, pet, venom, or environmental allergies, or allergies to oral medications (including the oral equivalents of injectable medications) are ***not*** *a contraindication or precaution to vaccination with either mRNA COVID-19 vaccine. The vial stoppers of these mRNA vaccines are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, as the mRNA COVID-19 vaccines do not contain eggs or gelatin, persons with allergies to these substances do not have a contraindication or precaution to vaccination.*

Observation periods following vaccination (for persons without contraindications to mRNA COVID-19 vaccines)

CDC recommends an observation period following vaccination with mRNA COVID-19 vaccines. Persons with a history of an immediate allergic reaction of any severity to a vaccine or injectable therapy and persons with a history of anaphylaxis due to any cause should be observed for 30 minutes. All other persons should be observed for 15 minutes."

Pfizer is independent of these recommendations.

<u>Potential Differentiation of Allergic Reactions, Vasovagal Reactions, and Vaccine Side Effects</u>

The ACIP interim clinical considerations also describe potential characteristics of allergic reactions, vasovagal reactions, and vaccine side effects following mRNA COVID-19 vaccine and makes recommendations on whether a person can receive a 2nd dose.

"In patients who develop post-vaccination symptoms, determining the etiology (including allergic reaction, vasovagal reaction, or vaccine side effects) is important to determine whether a person can receive additional doses of mRNA COVID-19 vaccines. The following table of signs and symptoms is meant to serve as a resource but may not be exhaustive, and patients may not have all signs or symptoms. Providers should use their clinical judgement when assessing patients to determine the diagnosis and management".[4]

Please see Table 1 below.

Table 1. Potential Characteristics of Allergic Reactions, Vasovagal Reactions, and Vaccine Side Effects[4]

Characteristic	Immediate Allergic Reactions (including Anaphylaxis)	Vasovagal Reaction	Vaccine Side Effects (Local and Systemic)
Timing after vaccination	Most occur within 15-30 minutes of vaccination	Most occur within 15 minutes	Median of 1 to 3 days after vaccination (with most occurring day after vaccination)
Signs and Symptoms			
Constitutional	Feeling of impending doom	Feeling warm or cold	Fever, chills, fatigue
Cutaneous	Skin symptoms present in ~90% of people with anaphylaxis, including pruritus, urticaria, flushing, angioedema	Pallor, diaphoresis, clammy skin, sensation of facial warmth	Pain, erythema or swelling at injection site; lymphadenopathy in same arm as vaccination
Neurologic	Confusion, disorientation, dizziness, lightheadedness, weakness, loss of consciousness	Dizziness, lightheadedness, syncope (often after prodromal symptoms for a few seconds or minutes), weakness, changes in vision (such as spots of flickering lights, tunnel vision), changes in hearing	Headache
Respiratory	Shortness of breath, wheezing, bronchospasm, stridor, hypoxia	Variable; if accompanied by anxiety, may have an elevated respiratory rate	N/A
Cardiovascular	Hypotension, tachycardia	Variable; may have hypotension or bradycardia during syncopal event	N/A
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea may occur
Musculoskeletal	N/A	N/A	Myalgia, arthralgia
Vaccine Recommendations			
Recommended to receive 2nd dose of mRNA COVID-19 vaccine?	No	Yes	Yes

Please note that Pfizer is independent of these recommendations.

Pfizer is unable to make any recommendations regarding for individual patients who may receive the Pfizer-BioNTech COVID-19 Vaccine; clinical judgment based on the medical history and the clinical status of a specific patient should dictate the appropriate actions to be taken.

REFERENCES

1. Emergency Use Authorization (EUA) Fact Sheet for Healthcare Providers Administering Vaccines including the Full EUA Prescribing Information. Pfizer/BioNTech.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 (**Identifier NCT04368728**). Available at: http://clinicaltrials.gov/ (Cited September 29, 2020)
3. Pfizer-BioNTech COVID-19 vaccine. Data on File (19). Pfizer Inc.
4. Advisory Committee on Immunization Practices (ACIP). Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States. Centers for Disease Control and Prevention website (Page last updated December 30, 2020). Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-manufacturer%2Fpfizer%2Fclinical-considerations.html (Last accessed January 04, 2021)