JYNNEOS and TPOXX for Monkeypox
VHA PBM Frequently Asked Questions (FAQ):
October 9th, 2022

VA Pharmacy Benefits Management Services

Background

In May of 2022, the World Health Organization reported on a rapidly spreading outbreak of Monkeypox infections outside of Africa, in non-endemic countries. Monkeypox is a rare zoonosis endemic to parts of Africa caused by an orthopoxvirus related to smallpox and transmitted from infected mammals, including squirrels, dormice and monkeys. An outbreak in 2003 in the U.S. was linked to pet prairie dogs imported from Africa. Human to human transmission can occur, through contact with infected bodily fluid, skin lesions, respiratory droplets or through contaminated objects. In the current outbreak, the biggest risk factor has been men who have sex with men who contract monkeypox on contact with skin lesions during sexual activity. The first U.S. case was reported on 5/18/22, in a patient returning from Canada. As of August 8, 2022, over 7000 cases have been identified in the U.S., and nearly all states have reported at least one case. On August 4th, the White House declared Monkeypox a national Public Health Emergency.

Monkeypox typically presents with a prodrome of fever, headache, lymphadenopathy, back pain, myalgia and/or asthenia beginning 5-21 days after infection. This stage is quickly followed by a diffuse rash, with lesions evolving from macules to papules, to vesicles, to pustules, often umbilicated, before they scab over and resolve. This stage can last for 2-4 weeks. Lesions can be seen on the hands and soles of the feet. Pictures of characteristic lesions and a detailed timeline of infection can be found on the CDC monkeypox information website. It is assumed that immunocompromised patients may have worse outcomes, although data with monkeypox are lacking. Immunocompromise was associated with severe complications after smallpox or vaccination with a replication-competent smallpox vaccine. Patients are contagious while the rash is present, until all lesions have fallen off and new skin has formed. Monkeypox should be suspected in any patient with a characteristic rash, including atypical genital lesions. Please see here for **CDC Case Definition**.

The information below is intended to provide guidance on use and acquisition of specific products for monkeypox for VHA clinicians. **MOST RECENT UPDATES ARE IN PURPLE FOR RAPID RECOGNITION OF CHANGES. October 1st update: VHA has been allocated a small supply of tecovirimat for internal distribution. Instructions on how to order and utilize the VA allocation are included in this update**

Use of JYNNEOS Vaccine for Prevention of Monkeypox

Two vaccines are currently available as pre- or post-exposure prophylaxis against monkeypox. JYNNEOS is a live virus, non-replicating vaccine against smallpox and monkeypox. ACAM2000 is a live *Vaccinia virus* vaccine inoculated into the skin, indicated for smallpox and is a derivative of the original smallpox vaccine, Dryvax, used for mass vaccination during smallpox eradication. JYNNEOS is currently preferred due to a lower risk of severe adverse events. This document will focus on JYNNEOS, as that is the primary vaccine in use at this time.

General considerations:

- **JYNNEOS** is a replication incompetent live-virus vaccine, FDA indicated for the prevention of smallpox and monkeypox in adults at high risk.
  - Vaccine effectiveness against monkeypox is inferred from immunogenicity in a clinical study and efficacy data from animal challenge studies.
  - No data exists on the efficacy of JYNNEOS as post-exposure prophylaxis.
  - Of note, each 0.5 mL dose may contain residual amounts of gentamicin and ciprofloxacin, and the vaccine does not contain preservatives.

- **Dosing and Administration**
  - JYNNEOS is FDA approved to be given as 2 subcutaneous (SQ) doses of 0.5mL each, 4 weeks apart, into the fatty tissue over the triceps in the upper arm.
    - Data from the manufacturer states that while it is not recommended to give the second dose before the minimum interval of 28 days, doses may be given up to 4 days before or up to 7 days after the recommended interval of 28 days. If the dose is delayed more than 7 days after the 28-day interval, it should be given as soon as possible. There is no need to restart the series.
    - Based on ACIP best practices, JYNNEOS may be administered without regard to timing of other vaccines. This includes simultaneous administration of other vaccines with JYNNEOS on the same day but at different anatomic sites.
  - Note: on 8/9/2022, the FDA authorized an alternate dosing regimen of JYNNEOS for adults under the Emergency Use Authorization process, as a way to extend the limited supply of vaccine to more high-risk individuals.
    - The EUA does not apply to the standard dose above, except for in children. For adults, the EUA dosing regimen of JYNNEOS is 0.1 mL to be administered intradermally (similar to a tuberculin skin test), with a second dose 28 days later.
    - The data to support the altered dosing regimen came from a Phase 2 study comparing an intra-dermal injection of a 0.1 mL of a liquid vaccine formulation (n=191) to a dose of 0.5 mL of the same liquid formulation (n=167) or 0.5 mL SQ of a lyophilized preparation (n=165), each given as two doses 28 days apart.
      - Of note, the age range was 18-38 years old, with an approximately even split of primarily white, non-Hispanic men and women.
      - Data in this study found that immunologic responses with intradermal injection were non-inferior to SQ administration
    - **In VHA, the alternative intradermal regimen is preferred for most patients to maximize supply (under EUA)**
    - **Individuals with a history of developing keloid scars should receive the standard subcutaneous regimen (FDA Approved)**

  - **Storage, Dose Preparation and Administration**
    - **Storage and Stability:**
      - The vaccine is available frozen and should be allowed to thaw and reach room temperature prior to administration.
        - When thawing directly from the freezer, use vaccine vials before the date marked on the carton
        - Once thawed, it can be stored refrigerated (36-46° F) **for up to 8 weeks**. *Of note, this information can be found on the CDC JYNNEOS Storage and Handling Summary but differs from language in both the JYNNEOS package insert and EUA Fact Sheet for Health Care Providers, which only allow for the vaccine to be kept for 12 hours refrigerated once thawed.*
        - **Do not re-freeze a vial once it has been thawed.**
      - **Room Temperature:** Unpunctured vials may be stored at room temperature (46-77° F) for up to 6 consecutive hours
      - Once the vial has been punctured it should be stored refrigerated and must be discarded **within 8 hours after first puncture**. CDC recommended beyond-use date labels to track storage times.
    - **Prior to administration, patients should be given the appropriate education material**
      - For those receiving the alternative intradermal regimen, patients should be supplied the EUA Fact Sheet for Recipients and Caregivers

- For those receiving the standard (FDA-approved) subcutaneous regimen, patients should be supplied the JYNNEOS Vaccine Information Statement (VIS)

- **Dose Preparation:**
  - Frozen vaccine should be allowed to thaw before using. If removing the vial from the refrigerator, let it stand at room temperature for 15 minutes prior to administration.
  - The upright vial should be swirled gently for at least 30 seconds prior to withdrawing the dose. It should be a milky, light yellow to pale white colored suspension. Do not use if the liquid is discolored or contains other particulate matter. The vaccine doses should be prepared immediately prior to administration to the patient.
  - **For EUA intradermal dosing (recommended for most patients):**
    - After cleaning the vial stopper with a new, sterile alcohol prep pad, withdraw 0.1 mL of vaccine into a sterile syringe with a 27 gauge, ¼ - ½ inch needle with a short bevel. **Always use a new, sterile needle and syringe for each injection**
    - *Note: if using low dead volume syringes and/or needles, 5 doses can be extracted from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 5 doses from a single vial.* ***Do not pool excess vaccine from multiple vials***
      - At 8 hours after first vial puncture, the vial must be discarded, regardless of how many doses were used.
      - For tracking purposes, the number of DOSES wasted should be tracked in addition to those given
    - The vaccine should be administered immediately by intradermal injection on the volar surface of the forearm. TMS training modules are available for intradermal injection (NFED 100275)
  - **For the standard (FDA approved) SQ regimen**
    - After cleaning the vial stopper with a new, sterile alcohol prep pad, withdraw 0.5 mL of vaccine into a sterile syringe with a 23-25 gauge, 5/8 inch needle with a short bevel.
    - The vaccine should be administered immediately by subcutaneous injection into the fatty tissue over the triceps of the upper arm. TMS training modules are available for subcutaneous injection.
- Regardless of which method is used, the patient should be observed after vaccination to monitor for the occurrence of immediate adverse reactions, including syncope. The duration of observation is
  - **30 minutes** for persons with a history of anaphylaxis to gentamicin, ciprofloxacin, chicken or egg protein (AND who are currently avoiding exposure to all chicken or egg products)
  - **15 minutes** for all other persons
- **For information on how to address vaccine administration errors and deviations, see the following CDC page: *Vaccine Administration Errors and Deviations | Monkeypox | Poxvirus | CDC* . Regardless of route of administration, all vaccine medication errors should be reported to VA ADERS, selecting the box for MedWatch report. For the intradermal route under the FDA EUA, JYNNEOS EUA should be included in the comments.**
- **Co-administration with other vaccines:**
  - Currently there are no data on administering JYNNEOS simultaneously with other vaccines. In most cases, CDC recommends JYNNEOS can be given on the same day as other vaccinations but at different anatomic sties.
  - If a monkeypox vaccine is recommended as prophylaxis in the setting of an orthopox outbreak, it should not be delayed because of recent administration of a COVID-19 vaccine (Moderna, Pfizer or Novavax).

- Some persons, especially young adult males might consider waiting 4 weeks after JYNNEOS or ACAM2000 vaccination, because of the observed risk for myo/pericarditis seen with both ACAM2000 and the Pfizer, Moderna and Novavax vaccines, and unknown risk of myo/pericarditis with JYNNEOS.

- **Interchangeability of SQ and Intradermal doses:** when necessary, adults who received standard SQ dosing (but without a history of keloid development) can receive the second dose intradermally.

- **Contraindications:** History of a severe allergic reaction (e.g. anaphylaxis) after a previous dose of JYNNEOS is a contraindication to subsequent doses. Referral to an allergist-immunologist should be considered to assess the risks versus benefits of the vaccine.
- **Precautions: Per CDC Guidance, the following situations should be considered precautions to JYNNEOS**
  - History of severe allergic reaction (e.g., anaphylaxis) following gentamicin or ciprofloxacin as JYNNEOS contains trace amounts of those antibiotics
    - After discussing the risks and benefits, if the decision to proceed is made, patients should be observed for 30 minutes after administration.
  - History of severe allergic reaction (e.g., anaphylaxis) to chicken or egg protein AND are currently avoiding exposure to all chicken or egg products
    - After discussing the risks and benefits, if the decision to proceed is made, patients should be observed for 30 minutes after administration.
  - Moderate to severe acute illness with or without fever
    - Consider deferring vaccination until the acute illness has improved
- **Warnings:**
  - Appropriate medical treatment must be available to manage possible anaphylactic reactions and patients who had a severe allergic reaction following exposure to any component of JYNNEOS may be at risk for severe allergic reactions. The risk of a severe reaction must be weighed against the risk from the disease.
  - Immunocompromised patients may have a diminished immune response to JYNNEOS
- **Adverse events**
  - Safety data for JYNNEOS comes from 7859 individuals across 22 studies who received at least one dose of vaccine. This included 7093 who were naïve to smallpox vaccine and 766 vaccine-experienced individuals.
  - Study 1 was a randomized, double-blind placebo-controlled study in the U.S. with smallpox vaccine naïve adults 18-40 years old who received 2 doses of JYNNEOS (n=3003) or placebo (n=1002), 4 weeks apart. In this study, the mean age was 28 years, approximately half were men and 77% were white. Solicited local and systemic adverse events are listed below for JYNNEOS vs. placebo, respectively.
    - **Injection site:**
      - **Pain:** 85% vs 19% (grade 3: 7% vs. 1%)
      - **Redness:** 61% vs. 18%
      - **Swelling:** 52% vs. 6%
      - **Induration:** 45% vs. 5%
      - **Itching:** 43% vs. 12%
    - **Systemic:**
      - **Myalgia**: 43% vs. 18% (grade 3: 3% vs. 1%)
      - **Headache:** 35% vs. 26%

- **Fatigue:** 30% vs. 20% (grade 3: 3% vs. 1%)
- **Nausea:** 17% vs. 13%
- **Chills:** 10% vs. 6%

- Adverse events were similar between dose 1 and 2, with the exception of injection site pain, which was more common after dose 1 (79%) than dose 2 (70%). The median duration for various adverse events ranged from 1 to 6 days.

- **Three studies (Study 2,3 and 4)** evaluated JYNNEOS in patients who previously were vaccinated with a smallpox vaccine. Across these studies local adverse events seen after any dose of JYNNEOS included redness (81%), pain (80%), induration (70%), swelling (67%) and itching (32%) at the injection site. Systemic adverse events included fatigue (34%), headache (28%), myalgia (22%), nausea (10%), chills (1%) and fever (0.5%).
- **Study 5** evaluated safety of JYNNEOS in HIV-infected studies in the US (naïve and smallpox vaccine experienced), in comparison to 97 non-HIV infected patients. In this study, solicited local and systemic adverse events were similar to the non-HIV individuals.
- **Study 6** evaluated safety of JYNNEOS in smallpox vaccine naïve patients with a history of or active atopic dermatitis (350 subjects with atopic dermatitis and 282 without). Solicited local and systemic adverse events were similar between the groups with and without AD with the exception of redness (61% vs. 49%), swelling (52% vs. 41%), chills (16% vs. 8%) and headache (47% vs. 35%).
- In the Phase 2 study comparing SQ with intradermal administration, most adverse events were similar between the groups, with the exception of injection site pain which was more common with SQ (100%) than ID (81%) and injection site itching, which was more common with intradermal (89%) than SQ (49%). Erythema was slower to resolve in many patients with intradermal administration. By 14 days, all of the SQ recipients had resolved erythema, while 44% in the intradermal group still had erythema, and a third of subjects had at least minimal induration or erythema at 180 days. A few patients developed small nodules or discoloration at the intradermal injection site.
- **Serious adverse events:** The integrated analysis of pooled data across all 22 studies evaluated serious adverse events (SAEs) through at least 6 months after the last vaccination. SAEs were seen in 1.5% of JYNNEOS vs. 1.1% of placebo recipients.
- Cardiac adverse events of special interest (AESI), such as ECG changes, elevated troponin-I or cardiac signs and symptoms were seen in 1.3% of JYNNEOS vs 0.2% of placebo recipients. The higher rate was primarily driven by asymptomatic post-vaccination troponin elevations. Six cases (0.08%) were considered causally related (tachycardia, T wave inversion, abnormal ECG, ST segment elevation, abnormal T wave and palpitations). None of these were considered serious.
- No myopericarditis was specifically reported. This is in contrast to ACAM2000, which has a documented risk of myopericarditis and according to the CDC is contraindicated in those with known underlying heart disease. Other important contraindications to ACAM2000 which are not noted with JYNNEOS include those with a history of atopic dermatitis or other active exfoliative skin conditions, immunosuppressed patient, pregnancy and breastfeeding (although known data on effects of JYNNEOS in pregnancy are limited to small animal studies).
- **There is limited human safety data given small numbers of patients who have received this vaccine. Providers should be alert to any unusual conditions that may be adverse vaccine events and report those to VA ADERS**

- **Vaccine Strategies for JYNNEOS in monkeypox:** vaccines may be useful in the current outbreak when given before or soon after exposure to the virus. The following information outlines CDC strategies to mitigate monkeypox.
  - **Pre-exposure prophylaxis (PrEP):**
    - At this time, the CDC has stated that most clinicians and laboratorians not performing the orthopoxvirus generic test, are not advised to receive vaccine PrEP, however broader vaccination of people who may be at risk may be recommended when more JYNNEOS is available.
    - For those at ongoing risk for exposure to virulent orthopoxviruses (such as laboratory workers who handle monkeypox or smallpox), the Advisory Committee on Immunization Practices (ACIP) recommends a booster dose every 2 years.

- **Post-exposure prophylaxis (Standard PEP):** Vaccine can be given after a high-risk exposure to monkeypox virus, and the sooner it is given, the better. The CDC recommends the vaccine be used within 4 days of exposure to prevent infection. Between 4-14 days after exposure, it may not be as effective. Beyond 14 days after exposure, benefits might outweigh risks after some clinical situations (e.g. a severely immunosuppressed person with a recent sex partner confirmed to have monkeypox). *Vaccination given after the onset of signs or symptoms of monkeypox is not expected to provide benefit.*
    - **HHS is allocating vaccine to jurisdictions for the following patients to be considered for monkeypox vaccine**
        - **Known contacts identified by public health case investigation, contact tracing or risk exposure assessments**
        - **Presumed contacts who may meet the following criteria**
            - **Know that a sexual partner in the past 14 days was diagnosed with monkeypox**
            - **Certain gay, bisexual or other men who have sex with men or transgender people, who have had any of the following within the past 14 days:**
                - **Sex with multiple partners (or group sex)**
                - **Sex at a commercial sex venue**
                - **Sex in association with an event, venue or defined geographic area where monkeypox transmission is occurring**
    - **For close contacts of known monkeypox cases:**
        - All contacts of persons confirmed to have monkeypox should be monitored for 21 days after their last exposure for symptoms of concern, including fever ≥ 100.4°F, chills, new lymphadenopathy or new skin rash. For more information on see the CDC monkeypox information
- **PEP++ or Enhanced PEP**
    - Enhanced PEP or PEP++ aims to reach those people with risk factors for exposure to monkeypox, even if they have not had documented exposure to someone with confirmed monkeypox. The CDC considers those with multiple sexual partners in the past 14 days in a jurisdiction with known monkeypox to be an appropriate indication for vaccine.
    - PEP++ may be a good public health strategy to reduce spread of monkeypox among high-risk populations but will be dependent on adequate supply of vaccine and distribution models to get it to those patients effectively. Note that The Administration for Strategic Preparedness and Response recommends that jurisdictions prioritize PEP first, and then if supply is sufficient to meet those needs, offer the vaccine to those who may have had a high-risk exposure (PEP++).
- It is recommended that facilities prioritize PEP first, before other vaccination strategies.
- Currently vaccine supply is not sufficient to recommend mass vaccination for the general public or all sexually active persons.

ACQUISITION OF MONKEYPOX VACCINES FOR VHA

- Monkeypox/smallpox vaccines are part of the U.S. Strategic National Stockpile (SNS) and are being distributed by HHS through State Health Departments in consultation with the CDC. HHS delivered small amounts of JYNNEOS and ACAM2000 to states for immediate use in mid-May. Currently they are in Phase 3 of distribution, with a plan to deliver approximately 1.6 million doses by the end of 2022. Allocations were determined by HHS considering both the burden of active monkeypox cases and at-risk population. For more information about distribution of vaccine by jurisdiction, see JYNNEOS Monkeypox Vaccine Distribution by Jurisdiction (hhs.gov) .

- **VHA is currently in a phased distribution plan, based on HHS allocations. Information on ordering of Monkeypox vaccine and the most recent distribution plan can be found at** PBM Monkeypox (MPX) Ordering (sharepoint.com) . While sites were initially instructed to reserve enough vaccine as second doses for each patient, HHS has entered into a new distribution plan, and facilities are NOT required to reserve second doses, so all current allocation can be used for first doses. VA will be able to re-order, once the entire VHA has approximately 10% of its initial allocation remaining.

- If sufficient vaccine is not available through VHA, acquisition should be coordinated with the local health departments to procure vaccine for a specific patient. Processes may vary by state, and healthcare providers are encouraged to contact their respective health departments to confirm appropriate procedures to request vaccine for a patient.
- For additional information, physicians can contact the CDC Emergency Operations Center at 770-488-7100 Monday through Friday 8 am to 4:30 PM EST. At other times, call 404-639-2888.
- Adverse events or medication errors associated with these vaccines should be reported to the VAERS (Vaccine Adverse Event Reporting System) program via VA ADERS (online https://vaww.cmop.med.va.gov/MedSafe_Portal/ or by fax 1-877-721-0366).

Treatment of Monkeypox with TPOXX in VHA

Per CDC Guidance, patients who should be considered for treatment include

- Those with severe disease (hemorrhagic disease, confluent lesions, sepsis, encephalitis or other conditions requiring hospitalization)
- Persons at HIGH risk for severe disease
  - Immunocompromised
  - Pregnant/breastfeeding women
  - Persons with one or more complications (e.g., secondary skin infections, gastroenteritis with severe nausea and vomiting, diarrhea or dehydration, bronchopneumonia, concurrent disease or other comorbidities)
  - People with a history or presence of atopic dermatitis or other exfoliative skin disorders (e.g. eczema, burns, impetigo, varicella zoster virus or herpes simplex virus infections, severe acne, psoriasis or Darier disease)
- Persons with monkeypox virus aberrant infections that include its accidental implantation in eyes, mouth or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)
- State/territorial health department authorities can direct requests for medical countermeasures to the CDC Emergency Operations Center (770-488-7100).

Tecovirimat (TPOXX) for Treatment of Monkeypox

- **Tecovirimat is an antiviral agent with activity against orthopoxviruses, including monkeypox virus. It is FDA approved for the treatment of smallpox based on animal models of improved survival, but is not FDA approved for other orthopoxvirus infections, including monkeypox. Currently it is available through HHS with an intermediate-size expanded access Investigational New Drug (EA-IND) protocol for treatment of non-variola orthopoxvirus infections (including monkeypox) in adults and children during an outbreak.**
  - **Mechanism of Action and Virology:** Tecovirimat prevents competent enveloped virions from being released by infected cells. In cell cultures, EC_{50} concentrations were 0.014-0.039 uM for monkeypox. Non-antagonistic antiviral activity with brincidofovir has been demonstrated in cell culture and animal models. Tecovirimat has a relatively low resistance barrier and amino acid substitutions in the target VP37 protein can confer large reductions in antiviral

activity. The possibility of resistance should be considered in patients who fail to respond to therapy or develop recrudescence after an initial period of responsiveness. Cross-resistance between tecovirimat and brincidofovir or cidofovir is not expected.

- **Efficacy:** human studies of tecovirimat against smallpox or monkeypox are not available. In studies of macaques and rabbits, treatment with 14 days increased survival from pox viruses was demonstrated (from 80-100% at day 4, versus 0% with placebo), and in a single study survival was 50% at day 6 vs. 0% with placebo.
- **Dosing/Administration/Storage:**
  - **Tecovirimat is supplied as 200mg capsules and a 20 mL, single dose 200mg vial for intravenous infusion.**
  - **The ORAL dose is 600mg every 12 hours for 14 days (with an increase to 600mg every 8 hours for those weighing 120 kg or more). Oral dosing is preferred and should be given <u>within 30 minutes of a full moderate or high fat meal.</u>**
    - If patients are unable to tolerate oral dosing, dilution with 0.9% sodium chloride or 5% dextrose is required. For those less than 120kg 20 mL of tecovirimat (200mg) should be mixed with 40mL of diluent **<u>in a syringe of suitable size</u>**. For those 120kg or greater, 30 mL of tecovirimat (300mg) should be mixed with 60 mL of diluent. Tecovirimat should NOT be diluted into prefilled infusion bags, due to concerns of leaching impurities from the administration equipment during dosing. It also should not be given as an IV bolus due to transient ataxia seen in nonhuman primates when dosed over 4 hours. *Patients should be changed to the oral formulation as soon as they are able to take oral medications and/or gastrointestinal pathology impacting absorption has resolved.*
    - The diluted infusion should be administered over 6 hours every 12 hours **<u>via syringe pump</u>**.
    - Diluted solution can be stored refrigerated for up to 24 hours, and for 4 hours at room temperature.
    - Duration of therapy is 14 days. According to the EA-IND protocol, in certain clinical situations, modifications to the dose, frequency and duration may be necessary depending on the individual patient's clinical condition, disease progression, therapeutic response and/or clinical judgement. These clinical decisions should include consultation with the CDC EOC (770-488-7100) and the FDA if necessary.
- **Pharmacokinetics:**
  - Absorption: Oral absorption is increased by 39% with food. Tmax is 6 hours with both oral and intravenous administration
  - Distribution: tecovirimat is approximately 80% bound to plasma proteins
  - Metabolism: hydrolysis, UGT1A1/1A4
  - Elimination: 73% excreted in urine, primarily as metabolites. Half-life approximately 20 hours.
- **Safety:**
  - **Contraindications:** tecovirimat INJECTION is contraindicated with severe renal impairment (CrCl < 30 mL/min) and should be used with caution in patients with mild or moderate renal impairment. There are no contraindications to oral tecovirimat.
  - **Warnings and Precautions:**
    - Hypoglycemia when co-administered with repaglinide: in a drug interaction study 10 of 30 patients co-administered experienced mild (6) or moderate (4) hypoglycemia which resolved after intake of food/oral glucose.
    - Risks of hydroxypropyl-β-Cyclodextrin in patients with renal insufficiency: it is known that clearance of cyclodextrin excretion is reduced in patients with renal impairment. Tecovirimat injection should be used with caution in patients with mild or moderate renal impairment.
  - **Adverse reactions:**

- Safety of ORAL tecovirimat comes from a phase 3 clinical trial in 359 health adults treated with 600mg orally at least once. Headache occurred in 12% of those receiving tecovirimat vs. 8% of placebo recipients. Nausea occurred in 5% and 4% respectively. Six of 359 patients discontinued tecovirimat due to adverse events. This included an abnormal EEG in one patient, mild palpable purpura in one patient, facial swelling, redness and pruritis in one patient, and 3 cases with multiple symptoms each, including gastrointestinal adverse events, decreased concentration, headache and dysphoria.
- Safety of intravenous tecovirimat comes from 26 adult subjects who received multiple 240mg doses by IV infusion vs. 6 who received placebo. Most adverse events occurred in a similar percentage of tecovirimat and placebo, although interpretation is hampered by a small placebo population. The only significantly greater adverse reaction was headache which occurred in 15% of tecovirimat vs. no placebo subjects. Infusion site pain was noted in 73% of tecovirimat vs. 67% of placebo recipients, swelling in 39% vs. 67%, erythema 23% vs. 67% and extravasation in 19% vs. 50%, respectively. Three patients discontinued therapy due to infusion site reactions (extravasation and swelling).

- **Drug-drug interactions:** Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19. However, effects are not expected to be clinically relevant for most substrates, other than an increase in repaglinide and decrease in midazolam concentrations.
- **Pregnancy and lactation:** No human data on use of tecovirimat in pregnancy or lactation are available. No embryofetal developmental toxicity was observed in mice or rabbits. In a mice study, tecovirimat was excreted in breast milk.
- **Impact on reproductive potential:** decreased fertility due to testicular toxicity (increased abnormal sperm and decreased sperm motility) was observed in male mice at approximately 24 times the human exposure. No effects of tecovirimat were noted on female fertility.
- **Dose adjustments:** No dose adjustment is required for patients with mild, moderate or severe hepatic impairment or mild or moderate renal insufficiency. Tecovirimat INJECTION but not tablets are CI in patients with severe renal insufficiency due to risks associated with accumulation of cyclodextrin vehicle.

➢ ACQUISITION OF TPOXX (TECOVIRIMAT) FOR MONKEYPOX FOR VHA

- Tecovirimat is an FDA approved antiviral for the treatment of smallpox currently available from the US SNS. It is currently available through HHS under an Intermediate size Expanded Access Investigational New Drug Protocol (EA-IND) that allows for use of tecovirimat for treatment of non-variola orthopoxvirus infections (including monkeypox) during an outbreak. The EA-IND provides an umbrella regulatory coverage, so clinicians and facilities do not need to request and obtain their own INDs. Expanded access is different than Emergency Use Authorization in that it is not "research" under the common rule definition but does require prospective RIB approval and IRB-approved informed consent from the patient or patient's legally authorized representative unless an exception from informed consent applies.
- The Office of Research and Development (ORD) and the Office of Research Oversight (ORO) have established a mechanism for VHA facilities to rely on the CDC Institutional IRB to participate in the expanded access program.
  - Once IRB processes are complete, they do not need to be repeated for subsequent patients.
  - Prospective VA R&D committee approval is required. *Note: Designated Review can be used by the R&D Committee for any non-emergency expanded use.* For sites without a R&D committee, contact ORD for further instructions on how to ensure approval can be met.
  - To participate in the TPOXX EA-IND program with CDC and VA ORD, each facility must submit an IRB Reliance Concurrence Form signed by the VA Facility Medical Director. Instructions on routing of the CDC IRB Concurrence form can be found on the ORD webpage below along with supporting documents and tools to support participating VA facilities.
  - **VA facility treating providers MUST follow the CDC's protocol for the TPOXX EA-IND. The current version of the CDC-IRB approved protocol, including the CDC-IRB approved informed consent document, CDC IRB approval documents and required and optional forms are included on the CDC's dedicated webpage for this program located at Information for Healthcare Providers on Obtaining and Using TPOXX (tecovirimat)**

for the treatment of Monkeypox.

- If a VA facility has already obtained IRB approval from their own or another facility, there is no requirement to transition IRB oversight to the CDC IRB. Questions about IRB oversight can be emailed to irbrelianceandsirbexceptions@va.gov
- **Detailed instructions and documents for implementing CDC IRB reliance can be found on the following ORD webpage:** Institutional Review Board (IRB) Oversight for CDC Tecovirimat (TPOXX) IND Expanded Access Program for Monkeypox: Instructions for CDC IRB Reliance For VA Facilities with Research Programs and Related Support of the CDC Tecovirimat Expanded Access Program
  - For additional questions regarding the CDC IRB reliance program for use expanded access tecovirimat program, please email them to VHACOORDrEGULATORY@VA.GOV For more information on VA R&D review components and any questions related to the EA-IND process.

- **Tecovirimat patient requests:**
  - **VA has been allocated a very limited supply of tecovirimat for internal distribution and does not anticipate receiving additional allocation in the near term. The process for distribution of VA's allocation is described in the VHA Tecovirimat Distribution Plan.** All requests are managed using the CDC process, which can be found here: Information for Healthcare Providers on Obtaining and Using TPOXX (Tecovirimat) for Treatment of Monkeypox | Monkeypox | Poxvirus | CDC
  - For each patient to be enrolled, providers will need to complete the required forms (see link above)
    - CDC Informed consent document
    - The patient intake form (return to CDC within 7 calendar days of tecovirimat initiation)
    - FDA form 1572 (return to CDC prior to initiation of tecovirimat to the extent feasible but no later than within 7 calendar days after initiation of tecovirimat)
    - If any serious or life-threatening adverse events and/or medication errors occur, report to CDC by completing a fillable PDF MedWatch form and returning to the CDC within 72 hours of awareness In addition, a**dverse events and medication errors associated with tecovirimat should be reported to the VAERS (Vaccine Adverse Event Reporting System) program via VA ADERS (online https://vaww.cmop.med.va.gov/MedSafe_Portal/ or by fax 1-877-721-0366)**
  - **The process for distribution can be found on the Tecovirimat ordering site:** Tecovirimat (TPOXX) (sharepoint.com)
    - **Because supply is current so limited, sites that opt-in to receive tecovirimat will receive a single, one-time shipment. To receive additional shipments, additional requests will need to be submitted. Orders will be entered into the HPoP system and automatically transferred to HHS's contracted distributor for fulfillment.**
      - **Tecovirimat is supplied in bottles of 42 capsules each**
      - **Two bottles will be needed for patients who weigh less than 120 kg**
    - **The pharmacy department must keep a perpetual inventory of all tecovirimat on hand within the pharmacy and number of bottles dispensed to patients daily. Inventory should be tracked as the number of bottles on hand.**
    - **Reporting requirements, instructions on handling damaged or wasted product, and detailed ordering instructions can be found on the PBM Tecovirimat ordering SharePoint** Tecovirimat (TPOXX) (sharepoint.com)

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