NC DEPARTMENT OF HEALTH AND HUMAN SERVICES

ROY COOPER • Governor
KODY H. KINSLEY • Secretary
HELEN WOLSTENHOLME • Interim Deputy Secretary for Health
MARK T. BENTON • Assistant Secretary for Public Health
Division of Public Health

Interim Guidance for NC Healthcare Providers
Tecovirimat in Treatment of Monkeypox*

Note that this information will be updated as the situation evolves or processes change

Purpose: To provide situational awareness for the current Monkeypox outbreak, as well as guidance for use of Tecovirimat in treatment of persons presumed to have or diagnosed with Monkeypox virus. Providers should be aware that Tecovirimat is available under an Expanded Access Investigational New Drug protocol, which involves request of the medication from NC Department of Health and Human Services (NC DHHS) and attendant enrollment process, as well as completion of federal regulatory paperwork (see Appendix B). Informed consent must be signed prior to initiation of therapy; other paperwork may be completed within 3 days.

Summary

- **Providers and facilities interested in prescribing tecovirimat for eligible patients under the EA-IND must request it through the NC Department of Health and Human Services using** this request form (see Appendix A for the complete Monkeypox Medical Countermeasures Request Process).
- Monkeypox (MPXV) is an infection caused by an orthopoxvirus. Cases are increasing rapidly in North Carolina. Symptoms may include fever, fatigue, lymphadenopathy, and a pimple- or blister-like rash. Anyone can get monkeypox, but many of the cases identified in the current outbreak have been in men who have sex with men.
- MPXV infection is often mild and self-limiting in the absence of specific therapy. However, the prognosis depends on multiple factors, such as previous vaccination status, initial health status, concurrent illnesses, and comorbidities. No deaths have occurred in the US outbreak, but some patients have experienced severe, debilitating pain and pruritis; as well as co-infection with STIs, making it important to evaluate need for treatment.
- Supportive care and treatment of symptoms should be initiated for all patients with monkeypox infection. This may include medicines or other clinical interventions to control itching, nausea, vomiting, and pain. See Interim Clinical Guidance for the Treatment of Monkeypox | CDC.
- Antiviral treatment of monkeypox infection should be considered for people with:
    - Severe infection
    - Illness complication
    - Risk factors for progression to severe infection (e.g. pregnancy or HIV)
    - Painful lesions of mouth, anogenital or other sensitive anatomical areas
    - Ocular involvement
    - Provider's clinical determination of need
- Tecovirimat (TPOXX or ST-246) is an antiviral medication available in oral and IV formulations through an expanded access Investigational New Drug (EA-IND) protocol for the treatment of monkeypox infection in children and adults. It should be considered broadly for treatment of MPXV and may be used empirically based on clinical indications.

Requesting Tecovirimat

- Tecovirimat is only available through the federal Strategic National Stockpile. **Providers and facilities interested in prescribing tecovirimat for eligible patients under the EA-IND must request it through the NC Department of Health and Human Services using this request form** (see Appendix A for the complete Monkeypox Medical Countermeasures Request Process).
- NC DHHS will submit Monkeypox medical countermeasure requests to ASPR/SNS on behalf of the requesting agency.
- SNS will contact the receiving POC(s) to confirm delivery times and location and then repackage for shipment. Typical turnaround time after CDC approval is 24-30 hours for shipment and delivery. TPOXX does not have the same cold chain requirements as the vaccines resulting in shorter delivery times.
- Requirements for EA-IND protocol can be found in Appendix B
- If you have further questions or are experiencing issues in prescribing or accessing tecovirimat for your patients, please use the SNS inbox at phpr.sns@dhhs.nc.gov.

Monkeypox

Monkeypox is a disease caused by infection with an orthopoxvirus. The monkeypox virus is part of the same family of viruses as smallpox. Monkeypox symptoms are like smallpox symptoms but milder and can include a flu-like prodrome followed by a rash. Prodromal symptoms might not develop or can occur concurrently with or after rash onset, and may include fever, headache, muscle aches, swollen lymph nodes, and fatigue. Patients may not experience the entire constellation of these symptoms.

The rash often starts in a mucosal area, including the mouth, anogenital or rectal areas, and may remain in a limited area or become more widespread to the face, torso, or extremities (including palms or soles). The initial rash has also been documented in other non-mucosal locations. Lesions may start as a macule and then progress to papule, vesicle, pustule, and then scab (see photo examples at Centers for Disease Control and Prevention (CDC) Monkeypox Clinical Recognition webpage).

Pain and pruritus may be prominent and disproportionate to rash appearance. Severe proctitis has been a presenting symptom and can be associated with tenesmus and rectal bleeding. Pain may be severe enough to interfere with basic functions such as eating, urination, and defecation and can cause significant patient distress.

Co-infections with sexually transmitted infections, group A strep pharyngitis, and other viruses (e.g., varicella zoster virus or VZV) have been reported. It is important to evaluate for and treat other potential infections as appropriate.

Testing and Reporting
Information on sample collection, transport, testing and reporting to local public health can be found in this NC DHHS provider memo.

Supportive Care

Supportive care includes maintenance of adequate fluid balance, pain management, treatment of bacterial superinfections of skin lesions and treatment of co-occurring sexually transmitted or superimposed bacterial skin infections. Providers should address these symptoms adequately and early to prevent hospitalizations.

Skin lesions should be kept clean and dry when not showering or bathing to prevent bacterial superinfection. Pruritus can be managed with oral antihistamines and inert, anti-irritant topical agents such as calamine lotion or petroleum jelly.

For oral lesions, compounds such "magic" or "miracle" mouthwashes (prescription solutions used to treat mucositis) can be used to manage pain. Oral antiseptics can be used to keep lesions clean (e.g., chlorhexidine mouthwash). Topical benzocaine/lidocaine gels can be used for temporary relief, especially to facilitate eating and drinking, but should be limited to recommended doses.

For painful genital and anorectal lesions, warm sitz baths lasting at least 10 minutes several times per day may be helpful. Topical benzocaine/lidocaine gels or creams at the recommended doses may also provide temporary relief.

Proctitis can occur with or without internal lesions and, though often manageable with appropriate supportive care, can progress to become severe and debilitating. Stool softeners such as docusate should be initiated early. Sitz baths, as described above, are also useful for proctitis, and may calm inflammation. Similarly, over the counter pain medications such as acetaminophen can be used. Pain from monkeypox proctitis may require prescription medications, use of which should be balanced with the possibility of side effects, like constipation. Proctitis may additionally be accompanied by rectal bleeding. Though rectal bleeding has been observed to be self-limited, patients with rectal bleeding should be evaluated by a healthcare provider.

Nausea and vomiting may be controlled with anti-emetics as appropriate. Diarrhea should be managed with appropriate hydration and electrolyte replacement. The use of anti-motility agents is not generally recommended given the potential for ileus.

Antiviral Treatment: Tecovirimat

Tecovirimat (TPOXX or ST-246) is an antiviral medication that is FDA-approved to treat smallpox. In animal studies, tecovirimat has been shown to decrease the chance of dying from infections with orthopox viruses when given early in the disease course. In people, efficacy studies have been limited to drug levels in blood and a few case studies. In a case series of people with monkeypox infection, one patient received tecovirimat with results suggesting tecovirimat might shorten duration of illness and viral shedding, though efficacy is unknown (Adler, 2022).

In the United States, Tecovirimat is not FDA approved for treatment orthopox infection. However, it is available through the Centers for Disease Control and Prevention (CDC) under a non-research, expanded

access Investigational New Drug (EA-IND) protocol that allows for the use of tecovirimat for primary or early empiric treatment of non-variola orthopoxvirus infections, including monkeypox, in adults and children of all ages. Informed consent is required for all patients treated with tecovirimat.

Considerations for Use of Tecovirimat

Tecovirimat should be considered broadly for treatment of monkeypox, and patient selection is at the discretion of the treating clinician under the EA-IND. Particularly for people with monkeypox virus aberrant infections that include accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus) Both oral and intravenous formulations are available. Empiric treatment can be considered if there is appropriate clinical indication prior to laboratory confirmation, especially in the context of limited or delayed testing. Use of tecovirimat does not factor into isolation timeframe.

- Assessment for use can be managed either in person or via telehealth visit.
- Informed consent must be signed prior to initiation of therapy; other paperwork may be completed within 3 days. Electronic signature is acceptable.
- Prescribing physicians can provide TPOXX under CDC's IRB approval (institutional IRB review is not necessary).

Situations where tecovirimat should be prioritized for use include:

- People with monkeypox virus aberrant infections that include accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)
- Patients with severe disease, defined by evidence of sepsis or other clinical evidence of viremia, and lesion location or type[a]
- Patients with evidence of illness complications[b] or patient hospitalization
- Patients at high risk for severe disease, defined as patients with severe immunocompromising conditions;[c] patients less than 8 years of age; patients who are pregnant or breastfeeding; patients with diseases that could increase risk of stricture or fistula such as inflammatory bowel disease; and patients with significant active exfoliative dermatologic conditions.
- Provider's clinical determination of need

Check CDC's Interim Clinical Guidance for the Treatment of Monkeypox for the most up to date treatment considerations.

[a] Lesion location or type: Confluent lesions, lesions in anatomical areas at special risk of scarring or stricture, such as those near or directly involving the eye, mouth, rectum, or urethra.
[b] Complications: Severe or difficult to control secondary bacterial infection (including sepsis), proctitis (particularly with tenesmus, challenges in pain control, or rectal bleeding), gastroenteritis with nausea/vomiting, bronchopneumonia, and encephalitis.
[c] Severe immunocompromising conditions include people living with HIV who are not virally suppressed or have active opportunistic infection; hematologic malignancy; history of solid organ transplantation; hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-

host disease or malignant disease relapse; any condition actively requiring chemotherapy, radiation, or continuous or high-dose systemic corticosteroids; and autoimmune disease requiring immunosuppression or with immunodeficiency as a clinical component.
[d] Significant dermatologic conditions include presence of atopic dermatitis or other active exfoliative skin conditions or infections (e.g., psoriasis, Darier disease [keratosis follicularis], eczema, impetigo, primary varicella, zoster, or herpes).

Contraindications

- Persons unwilling to sign informed consent documentation for treatment under EA-IND are ineligible.
- Those with a known allergy to the drug or its components.

Precautions

- Significant interactions have been reported in healthy adults with co-administration of repaglinide (hypoglycemia) and midazolam (decreased effectiveness of midazolam).
- Monitoring of renal function is recommended in pediatric patients < 2 years of age
- IV formulation should not be administered to patients with severe renal impairment (CrCl <30mL/min).

Absorption Considerations and Adverse Effects of Tecovirimat

Oral tecovirimat: ***Drug absorption of the oral formulation is dependent on adequate, concurrent intake of a full, fatty meal.*** Standard adult oral dosing of tecovirimat is 600mg every 12 hours for 14 days. For most adults, this will require taking 3 pills every 12 hours. Therefore, ability to tolerate oral intake of a full meal twice a day is required. Reported adverse effects include headache (12%), nausea (5%), abdominal pain (2%), and vomiting (2%). Neutropenia was found in one study participant.

IV tecovirimat: IV tecovirimat should not be administered to patients with severe renal impairment (CrCl <30mL/min). Oral formulation remains an option for this population. IV tecovirimat should be used with caution in patients with moderate (CrCl 30-49 mL/min) or mild (CrCl 50-80 mL/min) renal impairment as well as patients younger than 2 years of age given immature renal tubular function. Reported adverse effects of the IV formulation include infusion site pain (73%), infusion site swelling (39%), infusion site erythema (23%), infusion site extravasation (19%), and headache (15%).

Other Therapeutic Agents

Other therapeutic options are under investigation and include the antivirals cidofovir and brincidofovir, as well as Vaccinia Immune Globulin Intravenous (VIGIV). CDC is currently developing an expanded access protocol for brincidovofir (Tembexa). However, it is not currently available commercially or through SNS request. Additionally, cidofovir can be obtained through CDC's SNS, but it's use has been limited by serious renal toxicity. To date, use of VIGIV has no proven benefit in the treatment of monkeypox and it is not known if a person with severe monkeypox infection will benefit from VIGIV. More information and updates

on the status of these therapeutics in monkeypox treatment can be found on the CDC Monkeypox Treatment Information for Healthcare Professionals webpage.

References

- Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, Osborne JC, Rampling T, Beadsworth MB, Duncan CJ, Dunning J. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *The Lancet Infectious Diseases*. 2022 May 24. https://doi.org/10.1016/S1473-3099(22)00228-6
- CDC. Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Monkeypox Cases. https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html
- European Medicines Agency. Tecovirimat. https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga
- Food and Drug Administration. Tecovirimat package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214518s000lbl.pdf
- Titanji B, Tegomoh B, Nematollahi S, Konomos M, Kulkarni PA. Monkeypox - A Contemporary Review for Healthcare Professionals. *Open Forum Infectious Diseases.* 2022. https://doi.org/10.1093/ofid/ofac310
- World Health Organization. Clinical Management and Infection Prevention and Control for Monkeypox - Interim Rapid Response Guidance. June 10, 2022. https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1

Appendix A.

Monkeypox Medical Countermeasures Request Process		
Request Stage	**Action Tracker**	**Notes**
Need for MCMs	Agency identifies need for treatment: • Due to confirmed case of monkeypox • Desire to have a small quantity of treatment on hand in anticipation of a confirmed case of monkeypox	
Submit Request	Agency will submit the Monkeypox MCM Request Form with justification, logistics, and MCM items/amount	SNS Inbox will be monitored for requests M-F, 8 am to 5 pm Time-sensitive or clinical support needs after-hours need to use the Epi On-Call number at 919-733-3419
Review Process	Monkeypox Response Team vets the request and makes 1 of 2 decisions: • Approved- forward request to CDC for fulfillment • Denied- requesting agency will be provided with a justification for denial of fulfillment	
CDC Fulfillment	• CDC clinical team provides IND documentation and guidance via email to requestor along with distribution details	• Typical turnaround time after CDC approval is 24-30 hours for shipment and delivery. Shipments include complete course regimen

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MAILING ADDRESS 1902 Mail Service Center, Raleigh, NC 27699-1902
www.ncdhhs.gov • TEL: 919-546-1820 • FAX: 919-715-2246

Strategic National Stockpile Medical Countermeasures for Treatment of Monkeypox

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Name	Indication	Dosing & Administration	Availability	Storage and Handling	Notes
TPOXX tecovirimat	FDA approved for treatment of Smallpox in adults and pediatric patients weighing at least 13kg. **Expanded access protocol for monkeypox**	Oral and IV formulations Weight based dosing 14 day course of therapy	**SNS request**	Oral: 200mg capsules; 42 caps/bottle Stored at controlled room temp IV: 200mg/20mL vial Store refrigerated @ 2-8°C	TPOXX IV contraindicated in those with severe renal impairment TPOXX oral must be taken within 30 minutes after moderate/high fat meal No human data on use in pregnancy; no toxicity in animal reproductive studies
Vistide cidofovir	FDA approved for treatment of CMV retinitis in AIDS patients **Expanded access protocol for monkeypox**	5mg/kg IV once weekly x 2 weeks Must be administered with fluids and probenecid	**Commercially & SNS Request**	75 mg/mL in clear glass, single use vial Store at controlled room temperature 20-25°C	Causes severe nephrotoxicity Renal function monitored within 48 hours prior to administration No human data on use in pregnancy; embryotoxic in rats

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Vaccinia Immune Globulin VIGIV CNJ-016	FDA approved for the treatment of complications associated with vaccinia vaccination **Expanded access protocol for Monkeypox**	6,000 U/kg IV x 1 dose Higher doses can be given if patient does not respond	**SNS Request**	15mL vial containing > 50,000 U/vial Product may be stored frozen at or below 5°F (≤ -15°C) or refrigerated at 36 to 46°F (2 to 8°C)	No animal or human pregnancy data; Other immune globulins used in pregnancy w/o negative effects

Appendix B. Expanded Access IND protocol Information for Tecovirimat.

The information to complete and return to CDC include:

- **Informed consent** – obtained ***prior to treatment initiation***. (Pages 47-51 of IND Protocol)
- **Lesion samples for molecular testing** from at least 1 lesion prior to tecovirimat treatment, and samples from any new lesions that develop during or up to 7 days after completion of tecovirimat treatment. For CDC Form 50.34, indicate Poxvirus Molecular Detection (CDC-10515) for the test order (code).
- **FDA Form 1572** – To be completed by the responsible clinician/healthcare provider overseeing the patient's treatment. Please return within 3 calendar days of tecovirimat treatment initiation along with a CV of the treating physician. This requires an MD or DO license.
- **Patient intake form** to provide patient's baseline condition at the time of tecovirimat treatment decision. Complete the sections/fields that are applicable to the patient. As possible: if clinical labs (e.g., CBC with differential, UA, metabolic panel) are performed at baseline, please include a copy of the results. Please return within 3 calendar days of tecovirimat treatment to the extent possible. (Pages 55-60 of IND Protocol)

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- **Adverse event form** to report whether any adverse event(s) occurred during treatment with tecovirimat. Return to CDC at the end of patient's tecovirimat treatment course. Life-threatening or serious adverse events during tecovirimat therapy should be reported to CDC within 24 hours of occurrence or as soon as possible. (Page 62 of IND Protocol)
- **1 Outpatient Case Report Form** (Attachment 2B-Form D in the IND protocol) during tecovirimat therapy (e.g., Day 7) to provide clinical progress of the patient. If clinical labs (e.g., CBC with differential, UA, metabolic panel) can be performed during treatment, please include a copy of the results. (page 64-66 of IND Protocol)
- **1 Post Tecovirimat Treatment Form** (Attachment 2B-Form E in the IND protocol) to provide patient's clinical outcomes information after completion of treatment. If clinical labs (e.g., CBC with differential, UA, metabolic panel) can be performed at the conclusion of treatment, please include a copy of the results. (page 67-69 of IND Protocol)
- **Tecovirimat Product Accountability Form** to document product use and/or disposal following completion of treatment. (page 61 of IND Protocol)
- **Photos of lesions**, to the extent possible: at least 1 prior to tecovirimat treatment and 1 during treatment (between days 7 and 14) with dates of the photo(s) indicated. Photo(s) of any new lesions that develop during or up to 7 days after completion of tecovirimat treatment.

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