South African National Essential Medicine List Committee
Adult & Paediatric Hospital Level Medication Review Process
Component: Infections

Tecovirimat for the management of mpox infection: a summary of available evidence and interim recommendation pertaining to its use in South Africa

Date: 27 June 2024

Background: The National Department of Health (NDoH) has set up an Incident Management Team (IMT) to respond to the current mpox cases in South Africa. On the 26 June 2024, the National Institute of Communicable Diseases (NICD) reported sixteen laboratory-confirmed cases of mpox in South Africa since the outbreak of the disease in May 2024 (eight cases from KwaZulu-Natal, seven cases from Gauteng, and one from Western Cape). All cases were reported as male, aged between 23-43 years old. Only one of these 16 cases were not hospitalised. Three mpox-related deaths were reported at the end of June 2024.[1] There is currently no South African Health Products Regulatory Authority (SAHPRA) approved medicine for the treatment of mpox[2], however, treatment of patients with tecovirimat, an antiviral medicine, is currently being facilitated via a Section 21 SAHPRA approval on a per-patient basis, funded through a World Health Organization (WHO) limited donation program.

Tecovirimat (also known as TPOXX®) works by inhibiting activity of the orthopoxvirus VP37 protein and thus viral envelope formation[3]. Tecovirimat is licensed by the European Medicines Agency (EMA) for the treatment of smallpox, mpox, cowpox and complications from immunisation with vaccinia[4]. The United States Food and Drug Administration (FDA) in 2018 registered tecovirimat for the treatment of human smallpox disease caused by variola virus in adults and children but not for the treatment of other orthopoxvirus infections, including mpox[5]. Tecovirimat is not yet registered in South Africa.

There is currently a paucity of data regarding the efficacy of tecovirimat in the management of mpox. Some safety data have been obtained from observational studies. The NDoH program in collaboration with the NICD are in the process of developing guidelines for the clinical recognition, diagnosis and management of mpox in South Africa. In parallel the National Essential Medicines List Committee (NEMLC) assessed and summarised the available information relied upon by the WHO, the FDA and US Centers for Disease Control (CDC) and Prevention in their decisions to support tecovirimat use in the management of mpox as part of expanded access of an investigational new drug. Additionally, the EMA and United Kingdom (UK) National Health Service (NHS) recommendations and observational data available through an informal literature search are also summarised below.

Purpose: To understand currently available safety and efficacy evidence for tecovirimat in the treatment of mpox disease, in the context of the donation of limited quantities of tecovirimat by WHO.

Review of the Literature
This is an interim rapid summary statement and therefore a full medicine review process was not followed. An informal search was conducted using the WHO, FDA, CDC, EMA and NHS websites in early June 2024 to understand international guidance on mpox. Thereafter a non-structured search (also June 2024) was conducted on the topic of mpox, using PubMed, resulting in the retrieval of observational studies only.

Mpox: International recommendations given limited clinical evidence

<u>WHO Guidelines</u>
The WHO recommends that in patients with mpox, "it is preferable to use antivirals under randomized clinical trials (RCTs) with collection of standardized clinical and outcome data to rapidly increase evidence generation on efficacy and safety and, when not possible, antivirals may be used under expanded access protocols, such as MEURI (Monitored

Emergency Use of Unregistered and Investigational Interventions)".[3] Tecovirimat, brincidofovir and cidofovir were considered by the WHO.[3]

FDA

Tecovirimat may be used for people with severe small pox disease or who are more likely to get severely ill, like patients with weakened immune systems. In line with the CDC expanded access Investigational New Drug protocol the use of tecovirimat for the treatment of other orthopoxvirus infections, including mpox, is unapproved or investigational. There are no FDA-approved treatments for monkeypox virus infections, and no data establishing the safety or effectiveness of using tecovirimat to treat monkeypox in humans. However, based on the animal efficacy data that showed survival benefit over placebo in animal models, the FDA states that it may be reasonable to anticipate tecovirimat may provide benefit in treating some people with disease caused by orthopoxviruses, including the virus that causes mpox."[5]

US Centers for Disease Control and Prevention

"Oral tecovirimat to be made available for patients with mpox who meet eligibility criteria (e.g., have severe disease or involvement of anatomic areas that might result in serious sequelae or are at high risk for severe disease) under CDC's expanded access Investigational New Drug (EA-IND) protocol".[6,7]

European Medicines Agency (EMA)

Tecovirimat is licensed by the EMA for the treatment of smallpox, mpox, cowpox and complications from immunization with vaccinia.[8]

National Health Service (NHS)

In a rapid policy statement; the United Kingdom NHS indicated that tecovirimat could be used in hospitalised patients with mpox confirmed by polymerase chain reaction (PCR) testing; symptomatic with a syndrome compatible with ongoing monkeypox virus infection and meeting criteria for severe or complicated disease.

Summary of available efficacy & safety evidence

The WHO report (June 2022) highlighted one phase 3 placebo-controlled clinical safety study, which is summarised below[2]:

- A **Phase 3** expanded safety clinical trial:
  - Conducted in healthy volunteers
  - Tecovirimat (n=359) vs placebo (n=90)
  - Some reported adverse events (data available for 176 tecovirimat vs 32 placebo)[9] :
    - headache (80/176 vs 11/32),
    - nausea (22/176 vs 4/32)
    - abdominal pain (0/176 vs 1/32)

Due to the accelerated timeline and broad scope of the guideline, it was not feasible for the WHO to undertake a formal GRADE process (PICO questions; systematic reviews; formal documentation of values and preferences; and incorporation of consideration of costs, resources and feasibility). WHO indicated that they will aim to update this guidance with a GRADE-based, standard WHO guideline within 8–12 weeks of publication of the initial guidance, but an update is not yet available in the public domain.[3]

Planned randomised controlled trials

The US National Institute of Allergy and Infectious Diseases is currently conducting a randomised, placebo-controlled, double-blind study (Study of Tecovirimat for Human Monkeypox Virus; STOMP) of tecovirimat for the treatment of people with laboratory-confirmed or presumptive mpox disease. The estimated completion date is 30 May 2025.[10]

Observational studies

It should be noted that, although there is no established RCT evidence regarding safety and efficacy of tecovirimat in the treatment of mpox in humans, tecovirimat has now been widely used based on data from observational cohort studies.[11,12]. As the efficacy data is limited and the strength of this observational evidence is weak, data from well-conducted RCTs are required to firmly establish the efficacy of tecovirimat. Notwithstanding, observational data can be useful in characterising the safety of this product. An informal literature search conducted in PubMed in June 2024 highlighted evidence obtained from seven observational studies, which is summarised in Appendix 1.[11,12,13,14,15,16,17]

The studies summarised in Appendix 1 include three retrospective cohort reviews using medical records, one patient interview using public health surveillance data to recruit patients, one open-label non-randomized trial, one prospective observational study and one summary outlining nine case reports. Five studies were conducted in the United States, one in Italy and one in Japan. Despite the observational nature of the available studies and the challenge of small sample sizes, mpox infection was associated with higher rates of hospitalisation in severely immunocompromised patients and results appear to support early initiation of tecovirimat in immunosuppressed patients when a mpox diagnosis is suspected. Although one of these studies[16] demonstrated no improvement in healing time in treated vs untreated patients, tecovirimat appears to hasten symptomatic improvement in people with severe mpox and reduce viral shedding, thereby mitigating infection spread. Overall, treatment with tecovirimat was well tolerated. However, loss to follow-up was a concern in some studies.

Other/alternative antiviral agents

Potential alternative antiviral treatments for orthopoxviruses mentioned in the WHO Clinical Management and Infection Prevention and Control for Monkeypox Interim rapid response guidance (June 2022)[3] include cidofovir and brincidofovir. As reported by DeLaurentis *et al*.,[18] cidofovir has FDA approval as an antiviral against cytomegalovirus but also has activity against orthopoxviruses. However, its value is limited due to the need for intravenous administration and the potential for nephrotoxicity. Brincidofovir is FDA approved for the treatment of smallpox infection. It is an orally bioavailable lipid conjugate of cidofovir, a viral DNA polymerase inhibitor. It was reported in DeLaurentis *et al.* that three patients in the United Kingdom who received brincidofovir for the treatment of human monkeypox virus developed elevated liver enzymes, prompting early cessation of the drug.[18] Neither brincidofovir nor cidofovir are SAHPRA registered.[2]

NEMLC Proposal

1. NDoH Program should subscribe to the WHO and CDC recommendation and support access to tecovirimat, oral, on a compassionate basis for adult and paediatric patients via the limited WHO donation programme and Section 21 approval, for:
   - Hospitalised patients with confirmed, PCR positive mpox infection, with acute illness compatible with current mpox infection, noting that indications for hospitalisation might include:[7,19,20]
     - Severe immunocompromise
     - Extensive or spreading lesions
     - Other complications such as ocular, central nervous system, complex lesions in urogenital tract interfering with urination, lesions interfering with swallowing/breathing and intractable pain.

2. Clinicians treating patients (as per the SA NDOH Program Guidelines) in the public and private sector should collect case data, with the written permission of the patient or alternatively permission from next of kin (including delayed written consent), using the case report form (CRF) on the global clinical data platform (https://www.who.int/publications/i/item/WHO-MPX-Clinical_CRF-2022.3)[21] and other data requirements as per South African, WHO (e.g. suspected unexpected serious adverse reactions) and SA MEURI requirements.

3. The NEMLC should conduct a structured review of available evidence using predefined eligibility criteria, as an update to this review, as RCT data becomes available.

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Conflict of interest

The reviewers have no interests to declare pertaining to tecovirimat.

NEMLC Statement: 27 June 2024

Given the absence of randomised controlled trial data of safety and efficacy and the lack of registration of tecovirimat for the treatment of mpox in South Africa, the NEMLC cannot make a recommendation at this time for the inclusion of tecovirimat on the South African Essential Medicines List.

However, given the public health concern around the current outbreak of mpox, NEMLC supports the use of tecovirimat, through the limited WHO donation program, as an antiviral under investigation, in hospitalised patients who are confirmed PCR positive (not suspected) for mpox with acute illness compatible with current mpox infection, provided that case data is collected with the written permission of the patient or next of kin (including delayed written consent) and recorded and reported using the case report form (CRF) on the global clinical data platform and all other ethical and monitoring and evaluation data requirements as per South African, WHO (e.g. suspected unexpected serious adverse reactions) and SA MEURI requirements are met.

Appendix 1: Characteristics of selected observational studies

Citation	Study design	Population	Exposures & Control	Outcomes	Results	Comments
Aldred, et al. 2024[11]	Design: Retrospective cohort study 4 hospitals - Atlanta, Georgia, (June 1 to October 7, 2022 Funding: Grant P30AI050409: Emory Center for AIDS Research COI: Declared	People with HIV (PWH) with mpox who were treated with tecovirimat within 7 days of symptom onset	Treatment with tecovirimat within 7 days of mpox symptom onset. No tecovirimat & treatment after 7 days of symptom onset	Progression of mpox disease	N=112 PWH; n=56 tecovirimat within 7 days of symptoms & n=56 treated later/did not receive tecovirimat **Early tecovirimat group (demographics):** • Median (IQR) age: 35 (30-42) years • 54 (96.4%): cisgender men • 46 (82.1%) were Black, 10 (17.9%) other races **Late or no tecovirimat group (demographics):** • Median (IQR) age: 36 (32-43) years • 54 (96.4%): cisgender men • 49 (87.5%) Black; 7 (12.5%) other races/unknown race **Mpox disease progression** • 3 PWH (5.4%) in the early tecovirimat group vs 15 PWH (26.8%) in the late/no tecovirimat group (paired odds ratio, 13.00 [95%CI, 1.71-99.40]; P = .002)	• Possible confounding - fewer cases of severe mpox disease in the early treatment group. • Small sample size. • Timing of tecovirimat initiation. determined by prescription. • Adherence not measured. • Adverse events not reviewed.

Karmarkar et al. 2024[13]	Design:
	Patient interviews (November 2022 to February 2023) using public health surveillance data
	
	King County, Washington
	
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	COI: Declared
		Patients diagnosed with mpox (May to October 2022)	Tecovirimat	• Vaccination status
				• Comorbidities
				• Symptoms (self-reported dates for onset, first improvement date & illness resolution)
				• Association of tecovirimat with time to symptom improvement & illness resolution
				• Early (≤5 days from symptom onset) vs late tecovirimat (>5 days and ≤28 days from symptom onset)
					• N=465 diagnosed with mpox,
					• n=115 (25%) participated in study.
					  ○ 80 (70%) received tecovirimat
					  ○ 43 (37%) initiated tecovirimat early.
					  ○ 68 (59%) reported severe symptoms including (proctitis (n = 38 [33%]), rectal bleeding (n = 27 [24%]) & severe pain (n = 24 [21%]).
					Tecovirimat associated with:
					• Shorter time to symptom improvement (−5.5 days, P = .04) in severe illness
					• Longer time to symptom improvement in non-severe illness (0.9 day, P = .66).
					Early tecovirimat not associated with faster illness resolution, regardless of severity. Early initiation in severe disease may lead to faster illness resolution, though not statistically significant (−8.7 days; P = .11).
						Unclear impact of tecovirimat on disease progression and resolution.

Citation	Study design	Population	Exposures & Control	Outcomes	Results	Comments
Akiyama et al., 2024[14]	Design: Multi-center open-label double-arm trial (non randomised) (28 June 2022 to 30 April 2023). 7 sites in Japan Funding: Japanese MoH, Labor & Welfare (grant 20HA2005) AND Japan Agency for Medical Research and Development (grant JP22fk0108502) COI: None declared	Mpox patients Definitive diagnosis of smallpox/mpox, confirmed by positive polymerase chain reaction (PCR)	**Treatment:** Oral tecovirimat, 14-day course Dosing: Tecovirimat • 13 to <25 kg = 200mg • 25 to <40 kg = 400mg • ≥40kg = 600mg **Control:** Supportive treatment	**Primary outcome:** Negative PCR results for skin lesion specimens after 14 days of treatment **Secondary outcomes:** • Mortality • Ambulation • Resolution of rash	N=19, ≥13 kg at enrolment with a positive PCR positive n=19 (100%) tecovirimat n=0 control **Gender:** 19 (100%) males **HIV status:** 10 (52.6%) HIV positive **Severe disease:** 16 (84.2%) **Sexually Transmitted Infection (STI) status:** • 13 (68.4%) with history of STIs. • 2 (10.5%) concurrent STI **History of smallpox vaccination:** 0 (0)% **Study withdrawal: 5 of 19 (26.3%)** **Primary endpoint (n=15):** Negative PCR results (Ct value ≥ 40) for skin lesion specimens at 14 days after inclusion in the study: 9 (60%) **Secondary endpoints:** • Mortality: 0 (0%) • Total ambulation: 100% by 30 days • Adverse events (data available for 14 patients): 0 (0%) • Time from rash onset until resolution, median (IQR) (n=13): 24 days (16,31)	• Patients voluntarily chose the study arm they wished to join. This resulted in no patients in the control group. • Limited observational study which included measurement of objective outcomes. • Did not assess post-treatment lesions.
Vo et al. 2023[15]	Retrospective medical record review Clinical Sites in the Mount Sinai Health System (New York) Funding: No funding COI: Declared. One Author is a principal investigator for the STOMP trial	Suspected or confirmed mpox (1 July to 1 October 2022)	Tecovirimat	• Clinical characteristics	• N=130 received tecovirimat • n=80 PWH **Rates of recovery: PWH vs non-immunocompromised** • Similar rates of recovery, bacterial superinfections, and hospitalization **Severely immunocompromised vs non-severe immunocompromised** • n = 14; severely immunocompromised had a higher risk of hospitalization than those without severe immunocompromise (cohort inclusive of those with well-controlled HIV, excluding those without virologic suppression, n = 101): 50% versus 9% (P < .001). • Hospitalized patients (18 [13%]) mainly admitted for bacterial superinfections (44.4%), median hospital stay = 4 days. • Of those who completed follow-up (85 [66%]), 97% had recovery of lesions at time of posttreatment assessment. • No reported severe adverse events due to therapy.	• High rate of loss to follow-up. • Subjective prescribing. • Small sample size. • Results from electronic health record only at time of the initial visit. • Changes in the protocol. • Due to the density of hospitals and clinics in New York City, possibility that patients were hospitalised & followed up elsewhere.
Mazzotta et al. 2023[16]	Design: Prospective observational. (19 May – 29 September 2022). Clinical site: Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy	Hospitalized adult patients with lab-confirmed mpox	**Treatment** Oral tecovirimat 600mg twice daily for 14 days **Control:** No treatment Patients offered treatment based on international medical consensus.	• Clinical recovery • Time from symptom onset to complete clinical recovery by day 21.	N=41 patients enrolled • 19 completed tecovirimat treatment course • 22 untreated Of the 41 patients enrolled: • 100% male, 39 of 41 enrolled (95%) self-reported as men having sex with men. • 25 (61%) classified as severe disease. • Median age = 35 years (IQR 31-39) • 3 (7.3%) vaccinated for smallpox in childhood • 15 (37%) HIV+ • 7 (17%) on PrEP	• No randomisation. • Delays in treatment. • Small sample size.

Citation	Study design	Population	Exposures & Control	Outcomes	Results	Comments
	COI: Declared				**Main reasons for hospitalisation**: mucosal inflammation and/or superinfection of the lesions and/or management of severe pain from lesions **Median time from symptoms onset to tecovirimat initiation**= 10 Days (IQR 8-11) **Median time for clinical recovery:** • Treated: 23 days (IQR 18-29) • Untreated: 20 days (IQR 16-23)	
Seifu et al. 2023[17]	Design: Case reports August - September 2022 Voluntary reporting by healthcare workers to New York City Department of Health and Mental Hygiene, followed by completion of a survey detailing patient demographics, clinical characteristics an illness course Funding: None declared (potentially CDC) COI: Declared.	Patients presenting with new (post-treatment) lesions after completing treatment with tecovirimat	Tecovirimat	Improvement/resolution of lesions with initial tecovirimat course Resolution of lesions with and without additional tecovirimat treatment	N = 10 cases reported n = 9 patient surveys completed Post-treatment lesions were defined as the occurrence of new skin or mucosal lesions with probable or confirmed mpox, emerging ≤30 days after completing the recommended 14-day tecovirimat treatment course, after improvement or resolution of initial mpox lesions. Of the 9 patients for which the survey was completed: • 8 (89%) men and 1 (11%) transgender woman • 5 (56%) HIV positive • 4 (80% of HIV +) on antiretroviral therapy • 0 vaccinated for smallpox or mpox Median interval from mpox symptom onset to tecovirimat initiation = 9 days (6-16 days). **Treatment with initial tecovirimat treatment course:** • Worsening or no change in lesions: 0 (0%) • Mild improvement of lesions:1 (11%) • Significant improvement of lesion: 3 (33%) • Complete resolution of lesions: 5 (56%) • Difference between initial and post-treatment lesion severity score, median = -4 (range -10 to 1) **Post-treatment lesions (by treatment):** **Tecovirimat treatment (n=2)** *1 patient treated for 7 additional days and 1 treated for 14 additional days* Lesions resolved: 2 (100%) **No additional tecovirimat treatment given (n=7)** Lesions resolved: 6 (86%) Lost to follow-up: 1 (14%) • Median period for appearance of new lesions after completion of initial tecovirimat treatment = 13 days (2-30 days) • Post-treatment lesions were reported as less severe than initial lesions in 8/9 patients. • 6/9 patient's post-treatment lesions were tested for orthopoxvirus **Other STIs:** 6 (67%) patients tested for STIs; 1 tested positive for gonorrhoea and was treated **Adverse reactions:** 0 (0%)	• No active surveillance for post-treatment lesions, therefore the number of reported cases may be an under-representation. • Not all post-treatment lesions were tested for *Orthopox* virus or other potential aetiologies. • Analysis relied on provider-reported data, which may be subjective. • There is no indication of the reasons for the 2 patients being provided additional tecovirimat treatment compared to the other 7 patients who were not given additional treatment. The rationale for the length of the additional course (7 vs 14 days) was not described.
McLean J et al. 2022[12]	Design: Retrospective cohort study (June to August 2022	Individuals treated with tecovirimat for confirmed mpox infection	Tecovirimat	• Clinical presentation • Tecovirimat treatment outcomes	N= 154 treated individuals with confirmed mpox • 72/154 (47%) = PWH • 82/154 (53%) = HIV negative. **Gender:** n= 154 (male at birth) **Time from symptom onset to treatment initiation:** < in PWH (7.5 vs 10 days)	• No control group. • 46 patients were lost to follow up. reducing safety & clinical outcomes data.

Citation	Study design	Population	Exposures & Control	Outcomes	Results	Comments
	2 academic medical centers in New York City Funding: National Institutes of Health. COI: None declared	(defined as positive PCR) Exclusions: Individuals without confirmation of mpox infection from all analyses except for safety outcomes		• Tecovirimat safety outcomes	**N=42 without confirmed mpox infection** **Outcomes from initial follow-up visit:** Overall (N=134) • **Median days until first improvement:** 2.00 (range = 1-3.75) • **New lesions after 48 hrs:** 22 (18%) • **Required additional speciality consult:** 18 (15%) **Outcomes from post-treatment follow-up visit:** Overall (N=88) • **Pain resolved at end of treatment:** 73 (90%) • **Any persistent symptom at end of treatment:** 26 (32%) ○ Skin lesions = 13 (15.0%) ○ Rectal pain = 7 (8.0%) ○ Fatigue/malaise = 3 (3.4%) ○ Anal bleeding/discharge = 2 (2.3%) ○ Anala fissure = 2 (2.9%) ○ Dysuria = 1 (1.1%) ○ Other = 3 (3.4%) **Adverse events reported by patients with or without confirmed mpox virus infection (n=196):** • Serious adverse event 4 (2.0%) • No reported side effect 148 (75%) • 69 reports of side effects including: headache 12 (6.1%), nausea 10 (5.1%) and abdominal discomfort 8 (4.1%)	• Potential selection bias as having HIV could have been interpreted as a treatment indication. • PWH in the study had well-controlled disease, with viral loads <1000 copies/mL and CD4 > 200 cells/mm^3, therefore limiting insights on PWH with advanced disease.

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