Canada's
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CADTH Health Technology Review

Tecovirimat (TPOXX)

Sponsor: SIGA Technologies, Inc.

Indication: Treatment of human monkeypox

Drug Implementation Advice

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**.

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What Is the Unmet Need for the Treatment of Monkeypox?

With rapid growth and detection outside of endemic areas,[1] there is a need to develop a public health strategy for the management of human monkeypox. Vaccination is currently the primary measure to protect against the monkeypox virus. In Canada, vaccination has been recommended in specific populations as post-exposure prophylaxis (PEP) to reduce disease risk in individuals exposed to a case, and pre-exposure prophylaxis (PrEP) to reduce acquisition in groups at high-risk of occupational exposure in a research setting, as per the National Advisory Committee on Immunization (NACI) Interim guidance on the use of IMVAMUNE.[2] However, an unmet need remains for the treatment of an active progressive infection, especially for those with severe disease or at highest risk of progressing to severe disease.

What Is Tecovirimat (TPOXX)?

Tecovirimat (TPOXX) is an antiviral therapy that is approved in Canada for the treatment of human smallpox disease in adults and pediatric patients who weigh at least 13 kg. The mechanism of action of tecovirimat is to inhibit maturation and to prevent the release and spread of viral particles to other cells. Tecovirimat inhibits the activity of the orthopoxvirus VP37 protein and blocks the interaction of VP37 with cellular Rab9 GTPase and TIP47, which prevents the formation of the egress-competent enveloped virions necessary for cell-to-cell and long-range dissemination of a virus.[3] Tecovirimat is available as a 200 mg oral capsule. For individuals weighing more than 40 kg, the treatment dose is 600 mg (offered as three 200 mg capsules) taken twice daily orally for 14 days. Weight-based dose adjustment is also available for individuals who weigh less than 40 kg but more than 13 kg.[3]

How Did CADTH Approach This Review?

The aim of this CADTH review was to inform decision-making on the appropriate use of tecovirimat for the treatment of human monkeypox infection. CADTH convened an implementation advice panel (the panel) that spanned various disciplines and clinical settings with geographical representation across Canada. The panel captured expert advice through consensus and prioritized patient populations that were most likely to benefit from management for monkeypox infection. It was not the intent of the panel to address whether tecovirimat should be made available in Canada for the treatment of monkeypox.

What Is the Implementation Advice?

The panel suggests prioritizing the treatment of individuals who have a documented laboratory-confirmed diagnosis of monkeypox infection into 2 groups, as outlined in Table 1.

What Are the Limitations of the Review?

Important gaps in the available evidence include the lack of efficacy in well-controlled clinical studies in humans. The available evidence is limited to animal studies via the FDA Animal Rule and published case reports. Given that there is a lack of experience with tecovirimat use, the efficacy and safety in specific subpopulations of interest, including pediatric individuals weighing less than 13 kg, pregnant and lactating individuals, and those who are immunocompromised remains to be fully understood.

Table 1: Prioritization of Tecovirimat Treatment Based on A Tiered Risk Group Approach

Tier	Group
1	Treatment in individuals who have a documented laboratory-confirmed diagnosis and who: • have progressive infection with severe disease that requires significant supportive care (i.e., hospitalization) • are pregnant • have progressive infection and are severely[a] immunocompromised.[b]
2	Treatment in individuals who have a documented laboratory-confirmed diagnosis and have progressive infection at high risk of severe disease, which include those who: • are moderately[a] immunocompromised[b] • are infants and young children (≤ 10 years of age) • have atopic dermatitis with significant skin lesions.

[a] Defining moderately versus severely immunocompromised is at the discretion of the treating physician based on the following definition.

[b] Definition from COVID-19 vaccine – Canadian Immunization Guide: "Moderately to severely immunocompromised includes individuals with the following conditions: Immunocompromised due to solid tumour or hematologic malignancies or treatments for these conditions; solid-organ transplant and taking immunosuppressive therapy; hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy); immunocompromise due to chimeric antigen receptor (CAR)-T-cell therapy targeting lymphocytes; Moderate to severe primary immunodeficiency with associated humoral and/or cell-mediated immunodeficiency or immune dysregulation; HIV with AIDS-defining illness or tuberculosis diagnosis in last 12 months before starting vaccine series, or severe immune compromise with CD4<200 cells/uL or CD4%<15%, or without HIV viral suppression; recent treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (prednisone equivalent of ≥ 2 mg/kg/day or 20 mg/day if weight > 10 kg, for ≥ 14 days), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive; Chronic kidney disease on dialysis."[4]

Rationale for Decision

The scarcity of efficacy and safety data in a human population of those who have been treated with tecovirimat is a significant evidence gap, particularly in subpopulations of interest who are at higher risk of severe disease. The panel therefore relied more heavily on expert opinion where gaps in evidence have persisted. Evidence used to support the

implementation advice included the limited number of case reports of individuals treated with tecovirimat for orthopoxvirus, including vaccinia and monkeypox cases.

Given that monkeypox is a self-limiting and mild infection in most cases, the goals of treatment with tecovirimat were to avoid outcomes associated with severe disease, such as death and major supportive care (e.g., intensive care hospitalization). The panel agreed that tecovirimat should be reserved for treatment in patients who have progressive infection with severe disease that require significant supportive care or who are at a high risk of severe disease (i.e., pregnancy, immunocompromised, infants and young children, and atopic dermatitis with significant skin lesions).

For those at high risk of severe disease, the panel prioritized those who are pregnant and severely immunocompromised. Given the paucity of evidence, the panel could not comment on the safety and efficacy in these subpopulations but concluded that the benefits of treatment in these subpopulations likely outweigh the risks given the poor outcomes seen in practice. The panel determined it was important to differentiate between moderately and severely immunocompromised, as it was posited that those being actively treated with certain categories of immunosuppressive therapies would not be at the same level of risk as patients who have undergone organ transplants, for example. Children ages 10 and under were prioritized as the risk to small children is thought to be higher given that they have less body surface area and have increased risk of severe illness from infection, including 2 case reports in monkeypox for children aged 6 and 10.[5] Those with pre-existing skin lesions from atopic dermatitis were prioritized given their higher risk of requiring supportive care.

Panel Deliberation

The panel comprised 8 members representing internal medicine, critical care medicine, infectious diseases, emergency medicine, pediatrics, clinical immunology and allergy, geriatrics, ethics, pharmacy, and nursing from urban and rural clinical settings across Canada and met on June 23, 2022. The aim was to inform decision-making on the appropriate use of tecovirimat for the management of human monkeypox. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive treatment, with consideration for situations when supply may be limited.

The clinical value of tecovirimat was deliberated in the context of the increasing cases within Canada, as a disease of global public health importance. The implementation advice reflects the consensus of the panel based on the best available evidence for the use of tecovirimat. Given the lack of human clinical trials, and that most evidence is in the form of case reports, important gaps in the available evidence led the panel to use expert opinion to inform decision-making for the use of tecovirimat in the management of monkeypox. The panel also discussed ethical considerations for the judicious use of tecovirimat, particularly in scenarios of high demand for treatment. Drug costs or a health economic analysis were not considered.

Place of Therapy

Goals of Treatment

The primary goal of therapy is to avoid outcomes from severe disease, such as deaths and intensive care admissions. Examples of individuals with severe disease include, but are not limited to, hemorrhagic disease, confluent skin and mucous membrane lesions with functional implications, sepsis, pneumonitis, encephalitis, or other conditions requiring hospitalization. Tecovirimat should not be considered an alternative to supportive care, but as an adjunct in those whose disease is progressing despite the use of optimal supportive care measures.

Although there is a lack of clinical outcome evidence to support the use of tecovirimat beyond the primary goal, the panel suggested that potential secondary goals of treatment with tecovirimat could include the shortened duration of symptomatic disease, reduction of viral shedding and transmission, and reduction of long-term scarring. These are seen as areas where further data could provide a stronger clinical evidence base to inform goals of therapy and place in therapy.

Unmet Needs

Vaccination is recognized as an effective measure in protecting against monkeypox virus, and has been recommended in specific populations as PEP and PrEP as per the NACI interim guidance on the use of IMVAMUNE in the context of monkeypox outbreaks in Canada.[2]

The panel members agreed that the greatest unmet need is for treatment for individuals who have a documented laboratory-confirmed diagnosis; and who have severe disease that requires significant supportive care; has resulted, or may soon result, in hospitalization; or those that have progressive infection and are at high risk of severe disease (e.g., those who are immunocompromised).

The panel also identified an unmet need in individuals who are pregnant due to the increased risk to the fetus. Reported outcomes on the fetus of those diagnosed with monkeypox virus have included still births or pregnancy loss.[6]

The panel noted that the majority of those infected are healthy individuals and/or those with mild disease, and that these individuals are least likely to benefit from the drug and not achieve treatment goals.

There are currently ongoing clinical trials to evaluate the use of tecovirimat in different places in therapy (e.g., PEP); therefore, the use of tecovirimat may evolve with increasing data and experience.

Use of Tecovirimat in a Vaccinated Population

The use of tecovirimat in vaccine breakthrough infections has not been studied. Vaccinated individuals may be expected to have less severe disease; however, in the

absence of data on how much risk reduction they may have, if these individuals display progressive infection, the panel suggested they be eligible for treatment with tecovirimat if they meet criteria.

Prescribing Advice

- The panel advised that when tecovirimat is indicated, treatment with the drug should be initiated immediately, and in accordance with local approval processes, where established.
- The panel advised that when prescribing tecovirimat, care should be taken for people in which actual or potential drug-drug interactions exist, such as when tecovirimat is taken in combination with repaglinide and/or antiretrovirals.
- At the time of its review, the panel members agreed that there is a lack of evidence on the safety of tecovirimat in humans; therefore, individuals being treated with tecovirimat should be monitored for additional side effects or adverse drug reactions that may occur. Monitoring may include QT corrected for heart rate (QTc) prolongation if these individuals already have existing risk factors, as QTc prolongation has been reported in some animal studies.
- The panel agreed that tecovirimat dosing and duration of treatment should be in accordance with the product monograph.
- The panel advised that a patient-centred care discussion be held to discuss risks and benefits before prescribing tecovirimat to any patients, including the off-label nature of the treatment, and that informed consent should be obtained as part of the discussion. Furthermore, for individuals who are pregnant, a discussion should occur with their health care provider to properly determine whether tecovirimat is appropriate.
- The panel acknowledged the importance of supportive care. Initiating therapy with tecovirimat does not replace usual supportive care (e.g., hydration), as individuals may still be at risk for other complications (e.g., diarrhea).

Other Discussion Points

- Currently, there has been more than 3,400 documented cases of monkeypox globally, of which only 1 death (in Nigeria) has been reported.[1] This is important to consider when weighing the need for treatment for monkeypox, as it appears that recent cases have been self-limiting in nature.
- Use of tecovirimat as PEP in individuals at high risk of severe disease was considered by the panel; however, the absence of evidence on the safety and efficacy of tecovirimat in this circumstance did not support the use of tecovirimat in uninfected individuals outside the context of a clinical trial. In the future, based on evolving evidence, tecovirimat may be considered as PEP for higher risk individuals.
- The panel members identified individuals who are contraindicated to the vaccine as a potential unmet need. However, given the lack of evidence for the use of tecovirimat in PEP, based on expert opinion, the panel members agreed that tecovirimat should not be viewed as a replacement to vaccines.
- The panel discussed that people who have a documented laboratory-confirmed diagnosis of monkeypox may be advised against breastfeeding to minimize the risk of

transmission of the disease to infants, who have been highlighted as a vulnerable group who are at higher risk of poor outcomes. This should be discussed with the individual to ensure that this is consistent with their values and preferences.
While tecovirimat is not recommended for individuals weighing less than 13 kg, based on the product monograph, there is experience with use in the pediatric population, including a case report of a 28-month-old individual treated with tecovirimat. Currently, the sponsor is evaluating a weight-based dosing of the liquid formulation for people weighing less than 13 kg.

- The panel discussed that vaccination status is only 1 consideration when evaluating the risk of progressing to severe disease. Being unvaccinated is a risk factor that should be considered in combination with other factors (e.g., severity of disease, comorbidities, immunocompromised host) when assessing the need for treatment with tecovirimat. While vaccination with previous generations of the smallpox vaccine may offer protection from monkeypox, individuals may still not be fully protected given the timing of the vaccination (i.e., before 1980s).

Background

An overview of the details for the drug under review is provided in Table 2.

Table 2: Review Details

Item	Description
Drug product	Tecovirimat (as tecovirimat monohydrate) 200 mg capsule for oral administration
Indication	For the treatment of human monkeypox
Health Canada approval status	Approved for human smallpox
NOC date	November 29, 2021
Sponsor	SIGA Technologies, Inc.

NOC = Notice of Compliance.

Human Monkeypox

Monkeypox is a virus that was first discovered in monkeys in 1958 and later found in humans in the 1970s. Monkeypox is a viral zoonotic disease that occurs mainly in tropical rainforest areas of central and west Africa. While this virus was predominantly previously found in Africa, recent new cases have been identified in Europe and North America.[7]

Monkeypox virus is a member of the Orthopoxvirus genus in the family Poxviridae. Other viruses, such as smallpox and cowpox, also belong in the same family. As such, vaccines and therapeutics that have been developed for smallpox are thought to be effective for monkeypox as well.[8]

Table 3: Confirmed Cases of Monkeypox by WHO Region and Country[a]

Region	Confirmed	Death
African region	73	1[b]
Regions of the America	381	0
Eastern Mediterranean region	15	0
European region	2,933	0
Western Pacific region	11	0
Cumulative	3,413	1

[a] Data from January 1, 2022, to June 22, 2022, 17:00 CEST.[1]

[b] The single death occurred in Nigeria.

In Canada, the Public Health Agency of Canada (PHAC) first announced the confirmation of 2 monkeypox cases in Quebec on May 19, 2022. As of June 15, 2022, there are 159 confirmed cases in Canada with 132 cases in Quebec, 21 cases in Ontario, 4 cases in Alberta, and 2 case in British Columbia.[9] These numbers will likely continue to rise, and confirmed cases may be seen in other jurisdictions, as well.

Transmission of monkeypox mostly occurs through prolonged face-to-face contact; however, it can also be transmitted via bodily fluids. There is preliminary suggestion that clusters of cases are appearing in adult men who have sex with men.[10] Common symptoms include fever, headache, muscle aches, backaches, swollen lymph nodes, chills, and exhaustion.[11] A rash will often develop first on the face but can spread to other areas (e.g., genitals). The rash will evolve through different stages before forming a scab that will eventually fall off.[11]

Given the rapid transmission of monkeypox across Canada, a strategy is needed to prevent transmission, to contain outbreak, and to treat any confirmed cases. For those who have been previously vaccinated for smallpox (i.e., eligible for vaccine in 1980 or earlier), the degree of protection conferred from the smallpox vaccine against monkeypox infection may be up to 85%.[2]

According to WHO, the most recent case fatality ratio from monkeypox infection is about 3% to 6% in endemic areas.[12] The causes of death were also documented in high-risk groups, including infants, young children younger than 10, pregnant individuals, and immunocompromised individuals.[13]

In Canada, the PHAC National Emergency Strategic Stockpile (NESS) has a supply of vaccines and drugs in the event of a future smallpox emergency. The NESS stockpile includes IMVAMUNE and TPOXX capsules,[9] which would be available to address the monkeypox outbreaks in Canada.

NACI Interim Recommendations on Vaccines

In Canada, previous smallpox vaccines, including the freeze dried or frozen liquid formulations, were prepared from live vaccinia virus.[14] They were often associated with

many adverse side effects and were contraindicated for those who are immunocompromised as well as individuals with eczema or atopic dermatitis.[14]

More recently, a new vaccine with IMVAMUNE has been developed. It is a live-attenuated, non-replicating vaccine. It is also called Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). It is marketed under the brand name of JYNNEOS in the US and as IMVAXNEX in Europe.

On June 10, 2022, NACI issued interim guidance on the use of IMVAMUNE for PEP in adults with high-risk exposures to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. IMVAMUNE for PEP of monkeypox should be offered as soon as possible and within 4 days of last exposure, though can be considered for up to 14 days since last exposure.[2]

NACI also recommends PrEP for adults at high risk for occupational exposure in a laboratory research setting.

For special populations, NACI has also recommended that the IMVAMUNE vaccine be offered for the following populations:

- individuals who are immunocompromised due to disease or treatment
- individuals who are pregnant
- individuals who are lactating
- children and youth younger than 18 years
- individuals with atopic dermatitis.

NACI also recommends that IMVAMUNE (given as PEP or PrEP) should not be delayed due to recent receipt of a messenger RNA (mRNA) COVID-19 vaccine. If vaccine timing can be planned (i.e., before employment within a research laboratory), NACI recommends that IMVAMUNE be given at least 4 weeks after or before an mRNA vaccine for COVID-19.

Tecovirimat (TPOXX)

Mechanism of Action and Indication

Tecovirimat (TPOXX) is an antiviral therapy that is specific for orthopoxvirus. Tecovirimat works through the inhibition of the orthopoxvirus VP37 envelope wrapping protein activity and preventing the formation of egress-competent enveloped virions.[15]

Currently in Canada, tecovirimat is approved for the treatment of smallpox in adult and pediatric patients weighing at least 13 kg.

While tecovirimat is only approved for the treatment of smallpox, there is evidence from animal data to suggest it is likely to be an effective treatment for monkeypox, given that smallpox and monkeypox belong to the same family of orthopoxvirus.

Dosage and Administration

The usual treatment dose for individuals weighing more than 40 kg is 600 mg (three 200 mg capsules) taken twice daily orally for 14 days. Weight-based dose adjustment is necessary for those weighing less than 40 kg, but above 13 kg:

- 40 kg or greater takes a dosage of 600 mg twice daily for 14 days
- 25 kg to less than 40 kg takes a dosage of 400 mg twice daily for 14 days
- 13 kg to less than 25 kg takes a dosage of 200 mg twice daily for 14 days.

Tecovirimat is not recommended for those weighing less than 13 kg. However, the sponsor has provided a proposed weight-based liquid formulation dosing.[16] It is also recommended to take tecovirimat within 30 minutes after a moderate- or high-fat meal.[3]

Safety (Side Effects and Drug Interactions)

The most reported treatment-emergent adverse events (TEAEs) of tecovirimat were headache, nausea, abdominal pain, and vomiting. Most TEAEs were mild or moderate. Data for side effects was generated with healthy volunteers; therefore, information on adverse events in infected patients is lacking, and merits close monitoring of patients who are treated with tecovirimat.

Table 4: Adverse Reactions Reported in 1% or More of Healthy Adults Receiving At least 1 Dose of TPOXX 600 mg

Adverse reaction	TPOXX 600 mg N = 359 (%)	Placebo N = 90 (%)
Very common headache (≥ 10%)	12	8
Common nausea (≥ 1%)	5	4
Abdominal pain[a]	2	1
Vomiting	2	0

[a] Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain.[3]

Tecovirimat is a weak inducer of CYP3A4 and a weak inhibitor of CYP2C8 and CYP2C19 enzymes. These effects are not expected to cause any clinically significant drug interactions. According to the product monograph,[3] the 2 identified potential drug-drug interactions are with (1) repaglinide, where the serum concentration may be elevated with increased risk for hypoglycemia, and with (2) midazolam, where the serum concentration may be reduced, and for which the effectiveness of midazolam should be closely monitored.

It has also been reported that no clinically relevant drug interactions were observed when tecovirimat was administered with the following medications: bupropion, flurbiprofen, or omeprazole.[17]

On May 31, 2022, the British HIV Association released a rapid statement on monkeypox virus.[18] This statement listed tecovirimat as 1 of the treatment options for monkeypox and provided advice to verify any potential drug interactions via the Liverpool drug interaction site.[19]

According to the Liverpool drug interaction site, the following drug interactions have been listed as potential concerns:

Drugs that should not be administered:

- cabotegravir and rilpivirine (long acting) plus tecovirimat.

Potential clinically significant interaction (e.g., likely to require additional monitoring, alteration of drug dosage, or timing of administration):

- doravirine plus tecovirimat
- doravirine, lamivudine, and tenofovir DF plus tecovirimat
- dolutegravir and rilpivirine plus tecovirimat.

Potential weak interaction (e.g., additional action, monitoring, or dosage adjustment is unlikely to be required):

- atazanavir alone plus tecovirimat
- atazanavir and ritonavir plus tecovirimat
- atazanavir and cobicistat plus tecovirimat
- darunavir and ritonavir plus tecovirimat
- darunavir, cobicistat, emtricitabine, and tenofovir alafenamide plus tecovirimat
- bictegravir, emtricitabine, and tenofovir alafenamide plus tecovirimat.

QT prolongation has been reported with the use of tecovirimat. At this time, tecovirimat has not been added to the QT drug list at www.crediblemeds.org, a website with a database of medications known to cause QT prolongation. Based on internal documents provided by the sponsor, QT prolongation has not been seen with any of their clinical studies, including a specific 1 looking at the ECG effects with a supratherapeutic dose of tecovirimat. It was noted only in an animal study (e.g., beagle) where prolonged QT interval was observed in 1 incident.[16]

Recommendations From International Health Technology Assessment or Other Jurisdictions

While tecovirimat is officially approved for the treatment of smallpox, its use in monkeypox has been recommended or endorsed by various regulatory bodies and/or health technology agencies.

In the US, the Centers for Disease Control and Prevention has released an interim guidance for which tecovirimat is 1 of the several treatment options that can be considered for human monkeypox treatment.[20]

The Centers for Disease Control and Prevention guidance for tecovirimat use was outlined under the expanded access investigational new drug protocol during 2022 US monkeypox cases. According to this guidance, tecovirimat may be considered in the following situations:

- with severe disease (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization)
- for those who are at high risk of severe disease:
    - people with immunocompromised conditions (e.g., HIV and AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplant, therapy with alkylating agents, antimetabolites, radiation, tumour necrosis factor inhibitors, high-dose corticosteroids, being a recipient with hematopoietic stem cell transplant < 24 months post-transplant or ≥ 24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component)
    - pediatric populations, particularly patients younger than 8 years
    - pregnant or breastfeeding individuals
    - people with a history or presence of atopic dermatitis, people with other active exfoliative skin conditions (e.g., eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease [keratosis follicularis])
    - people with 1 or more complications (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea, vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities)
- with aberrant infections involving accidental implantation in eyes, mouth, or other anatomic areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus).

The European Medicine Agency has also approved the use of tecovirimat for smallpox, monkeypox, and cowpox. Based on animal studies, the European Medicine Agency also considers tecovirimat to be effective in reducing mortality caused by orthopoxviruses, which includes smallpox, monkeypox, and cowpox.[21]

Recently, the UK Health Security Agency has also released recommendations on pre- and post-exposure vaccination with the MVA-BN vaccine during a monkeypox incident.[22] However, no specific recommendation for tecovirimat is publicly available as of yet.

In Canada, only Ontario and Quebec have issued some interim guidance. In Quebec, where the number of cases of human monkeypox is highest, the smallpox vaccines have been deployed and offered to affected individuals.[23] The Quebec Immunization Committee has authorized the use of IMVAMUNE within 4 days of exposure for individuals with high risk contacts of confirmed or probable cases. A second dose may be given only if the risk of exposure is still present 28 days later. However, no guidance on the use of tecovirimat for the treatment of monkeypox has been published.

In Ontario, the Ministry of Health has issued a *Questions and Answers (Q&A) for Monkeypox Interim Vaccine Guidance for Post-Exposure Prophylaxis (PEP) and How to*

Access Tecovirimat.[24] It provides guidance on offering post-exposure vaccine with similar criteria as Quebec for high-risk individuals. It also offers a mechanism for accessing tecovirimat. However, no specific criteria have been provided for when tecovirimat should be used.

Other Treatment Options for Human Monkeypox

In addition to tecovirimat, other treatment options are also available, including cidofovir and vaccinia immunoglobulins, both of which require IV administration and are not readily accessible. There are also documented cases of resistance to cidofovir[25] as well as hydration requirements. In the US, brincidofovir may be available. It is a prodrug of cidofovir and available as an oral formulation. However, brincidofovir is not approved for use in Canada[26] and patients who were treated with brincidofovir were reported to have transaminitis.[27]

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tecovirimat. No filters were applied to limit the retrieval by study type. The search was completed on June 10, 2022, and limited to English-language documents. Retrieval was not limited by publication date.

Summary of Evidence

FDA Animal Efficacy Rule and Its Relevance for Tecovirimat

In 2002, the FDA established the Animal Rule (Code of Federal Regulations title 21, part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.[28]

The Animal Rule is intended to support drug development of therapies where clinical efficacy trials are not feasible due to ethical concerns. However, there are strict guidelines to follow; therefore, the US FDA will recognize evidence from animal studies only when all of the following criteria are met:[29]

- there is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention and substantial reduction by the product

- the effect is demonstrated in more than 1 animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans
- the animal study end point is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
- the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allow selection of an effective dose in humans.

Because smallpox is potentially fatal and studies with variola virus in humans would not be permitted, tecovirimat was approved via the Animal Rule.

Health Canada Extraordinary Use New Drugs Regulatory Pathway

In 2011, Canada's Food and Drug Regulations were amended to include a pathway for Extraordinary Use New Drugs (EUNDs), where due to logistical or ethical reasons, it is not possible for the sponsor to conduct human clinical trials.[30] The EUND regulatory pathway was developed for cases where there is limited clinical information and standard regulatory pathways for authorization cannot be used. This regulatory pathway allows sponsors to use results of animal studies, as well as results from human safety and efficacy data that are available. Drugs approved through the EUND pathways are monitored more extensively for clinical safety and effectiveness in the post-market phase.[30]

A manufacturer of a new drug may file an EUND submission for the new drug if the following criteria are met.[30]

- the new drug is intended for
  - emergency use in situations where persons have been exposed to a chemical, biological, radiological, or nuclear substance and action is required to treat, mitigate, or prevent a life-threatening or other serious disease, disorder, or abnormal physical state, or its symptoms, that results, or is likely to result, from that exposure, or
  - preventive use in persons who are at risk of exposure to a chemical, biological, radiological, or nuclear substance that is potentially lethal or permanently disabling; and
- the requirements set out in paragraphs C.08.002(2) (g) and (h) of the Food and Drug Regulations cannot be met because
  - exposing human volunteers to the substance referred to in paragraph (a) would be potentially lethal or permanently disabling, and
  - the circumstances in which exposure to the substance occurs are sporadic and infrequent.

In Canada, tecovirimat is authorized under the EUND pathway.

Nonclinical Animal Efficacy Studies

As part of the FDA requirements, 4 pivotal studies in nonhuman primates and 2 pivotal studies in rabbits were conducted. The primary end point was survival. In the nonhuman primate studies, cynomolgus macaques were lethally challenged by IV with 5 x 10^7 plaque-forming units of monkeypox virus. Tecovirimat was administered orally at 10 mg/kg dose for 14 days, starting at day 4, 5, or 6 post-challenge.[31]

In the studies with rabbits, they were lethally challenged intradermally with 1,000 plaque-forming units of rabbitpox virus. Tecovirimat was administered orally at 40 mg/kg, starting at day 4 of post-challenge.[31]

All animals were noted for clinical signs of disease (e.g., onset of lesions) by day 4 post-challenge. Survival was monitored for 3 to 6 times the mean time to death for untreated animals in each model. As noted in Table 5, all but 1 subject did not survive from the placebo group. However, the animal subjects from the tecovirimat group had a survival that ranges between 50% and 100%. The lower survival rate appears to be related to later treatment initiation.

Table 5: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

Study	Treatment initiation	Survival percentage		P value	Survival rate difference (95% CI)[a]
		Placebo	Tecovirimat		
Cynomolgus macaques					
AP-09-026G	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8% to 99.5%)
FY10-087	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1% to 100%)
SR10-037F	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5% to 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5% to 99.6%)
	Day 6		50% (3/6)	0.1231	50% (−28.3% to 90.2%)
SR10-038F	Day 4 (3 doses)	25% (1/4)	50% (2/4)	0.3643	25% (−51.0% to 83.0%)
	Day 4 (5 doses)		100% (6/6)	0.0141	75% (8.1% to 99.4%)
	Day 4 (7 doses)		100% (6/6)	0.0141	75% (8.1% to 99.4%)
	Day 4 (10 doses)		80% (4/5)	00972	55% (−20.9% to 93.7%)
NZW rabbits					
SR14-008F	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
SR13-025F	Day 4	NA	88% (7/8)	NA	NA

CI = confidence interval; NA = not applicable; NZW = New Zealand White.

[a] Exact 95% CI based on the score statistic of difference in survival.

Source: Product monograph.[3]

Other Animal Studies

In addition to the animal studies mandated by the FDA to establish efficacy of tecovirimat, other animal studies have been published evaluating the use of tecovirimat for smallpox or monkeypox. Some of these studies are summarized in Appendix 1.

Studies for Safety, Tolerability, and Pharmacokinetics

Once the efficacy of tecovirimat had been established in animal studies, a placebo-controlled pharmacokinetic and safety trial was conducted in adult volunteers.[31] This expanded safety trial was a multicenter, randomized, double-blind, safety trial involving healthy volunteers 18 to 79 years of age. A lead-in cohort of 40 participants was randomly assigned in a 4:1 ratio, in either a fed or a fasting state, to receive 600 mg of tecovirimat administered orally twice daily or matching placebo. Once safety and pharmacokinetic data confirmed sufficient levels in blood, the trial was expanded to evaluate safety by randomly assigning an additional 412 participants at 11 sites to receive tecovirimat or placebo in the fed state only.

Table 6: Summary of Baseline Characteristics of Patients

Patient characteristic	Tecovirimat (n = 359)	Placebo (n = 90)	Total (n = 449)
Sex, n (%)			
Male	148 (41)	36 (40)	184 (41)
Female	211 (59)	54 (60)	265 (59)
Race, n (%)			
White	249 (69)	62 (69)	311 (69)
Black	101 (28)	26 (29)	127 (28)
Asian	3 (1)	1 (1)	4 (1)
American Indian or Alaska Native	3 (1)	0	3 (1)
Native Hawaiian or other Pacific Islander	1 (<1)	1 (1)	2 (<1)
Other	2 (1)	0	2 (<1)
Ethnic group, n (%)			
Hispanic or Latino	43 (12)	5 (6)	48 (11)
Not Hispanic or Latino	315 (88)	85 (94)	400 (89)
Other	1 (<1)	0	1 (<1)
Age, yr			
Mean[a]	40.4 ± 15.7	41.9 ± 15.8	40.7 ± 15.7
Median	38.0	40.5	39.0
Range	18 to 79	18 to 80	18 to 80
Weight, kg			
Mean[a]	88.6 ± 22.8	89.7 ± 29.2	88.8 ± 24.2
Median	85.4	84.0	85.1
Range	49.1 to 188.0	51.4 to 240.6	49.1 to 240.6

Patient characteristic	Tecovirimat (n = 359)	Placebo (n = 90)	Total (n = 449)
Height, cm			
Mean[a]	169.3 ± 9.4	168.7 ± 9.0	169.2 ± 9.3
Median	168.7	168.2	168.7
Range	144.7 to 194.3	152.4 to 190.5	144.7 to 194.3
Body-mass index			
Mean[a]	30.9 ± 7.6	31.5 ± 9.7	31.0 ± 8.1
Median	29.4	29.0	29.3
Range	17.4 to 61.1	19.5 to 78.1	17.4 to 78.1

[a] Plus-minus values are mean plus standard deviation.

Source: Grosenbach et al. 2018[31] From N Engl J Med, Grosenbach DW, Honeychurch K, Rose EA, et al., Oral Tecovirimat for the Treatment of Smallpox, Volume 379, Page 44-53. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

From this study, the authors concluded that the exposures achieved with a dose of 600 mg twice daily exceeded the efficacious exposures in nonhuman primates. Most reported adverse events were mild, and all events, with the exception for the death, resolved without sequelae. The most common adverse event was headache. Discontinuation of the trial was rare. Breakdowns of the adverse events are reported in Table 4 and Table 7.

Table 7: Adverse Events That Occurred or Worsened During Receipt of Tecovirimat or Placebo in the Overall Summary Safety Population

	Tecovirimat (n = 359)		Placebo (n = 90)		Total (n = 449)	
Type of event[a]	Number of participants (%)	Number of events	Number of participants (%)	Number of events	Number of participants (%)	Number of events
Any event	134 (37.3)	318	30 (33.3)	68	164 (36.5)	386
Event related to the trial drug	71 (19.8)	176	15 (16.7)	32	86 (19.2)	208
Event leading to discontinuation of trial drug	6 (1.7)	16	2 (2.2)	3	8 (1.8)	19
Serious events and events leading to death	1 (0.3)[b]	1	0	0	1 (0.2)	1

[a] The adverse events considered here included any newly occurring event or previous condition that increased in severity or frequency since administration of the first dose of tecovirimat or placebo.

[b] The death was due to a pulmonary embolus that was judged by the investigators not to be related to tecovirimat.

Source: Grosenbach et al. 2018[31] From N Engl J Med, Grosenbach DW, Honeychurch K, Rose EA, et al., Oral Tecovirimat for the Treatment of Smallpox, Volume 379, Page 44-53. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Evidence for Use in Orthopoxvirus

In a study by Yu J et al.,[25] a systematic review was conducted to identify relevant studies evaluating the efficacy and safety of various antivirals against orthopoxviruses. A total of 23 cases have been identified describing human cases of orthopoxvirus infection treated with antivirals from 1980 to 2019. The majority of the cases were affiliated with vaccinia

infections with 1 case associated with cowpox infection. No monkeypox case was identified via this systematic review.

According to this systematic review, various drugs have been used for the treatment of vaccinia infections in humans. These include cidofovir, brincidofovir, vaccinia immunoglobulins, tecovirimat, and trifluridine ophthalmic solution. The most common treatment was vaccinia immunoglobulins.

Among the identified cases, there were 3 case reports that described the use of tecovirimat. A summary of key details is provided in Table 9.

Evidence for Use in Human Monkeypox

There have been 2 case reports published so far describing the use of tecovirimat in human monkeypox.

Retrospective Observational Study in the UK

Adler et al. recently published results of a retrospective observational study describing the clinical features and management of human monkeypox with tecovirimat as well as brincidofovir.[27] In this study, 7 patients were identified to have confirmed human monkeypox. Five patients were in isolation for 3 weeks. Three patients were treated with brincidofovir (200 mg once a week) and 1 patient was treated with tecovirimat (600 mg twice daily for 2 weeks). The patient treated with tecovirimat was reported to have a shorter duration of viral shedding and illness (10 days of hospitalization) compared with the other 6 patients.[27] The 3 patients who were treated with brincidofovir developed transaminitis that resolved with treatment discontinuation. The 1 patient treated with tecovirimat did not report any adverse effects.

Table 8: Summary of the Clinical Course and Response to Treatment in 7 Patients With Monkeypox

Course or response	2018			2019	2021		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Site of HCID unit	London	Liverpool	Newcastle	London	Liverpool	Liverpool	Liverpool
Age range, years	30 to 40	30 to 40	30 to 40	40 to 50	30 to 40	0 to 2	30 to 40
Sex	Male	Male	Female	Male	Male	Female	Female
Transmission rank	Isolated	Index	Secondary	Isolated	Index	Secondary	Tertiary
Country of acquisition	Nigeria	Nigeria	UK	Nigeria	Nigeria	UK	UK
Smallpox vaccination history	None	None	MVA-BN 6 days post-exposure or 12 days pre-illness	None	None	None	None

Course or response	2018			2019	2021		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
HIV, hepatitis B, and hepatitis C status	Negative	Negative	Negative	Negative	Negative	Not tested (parents negative)	Negative
Prodrome	Fever and night sweats (2 days)	Fever and groin swelling (4 days)	Coryzal illness (1 day)	Fever and headache (2 days)	None	None	None
Lymphadenopathy	Yes	Yes	No	Yes	Yes	Yes	No
Approximate maximum number of concurrent lesions	150	100	32	100	40	30	10
Distribution of lesions	Face, scalp, trunk, limbs, palms, glans penis, and scrotum	Face, trunk, limbs, palms, soles, and scrotum	Face, trunk, hands (including nail bed), and labia majora	Face, scalp, trunk, limbs, penile shaft, palms, and soles	Face, trunk, limbs, palms, and penile shaft	Face, trunk, arms, and legs	Face, trunk, arms, and hands
Complications of illness	Low mood and emotional lability; ulcerated inguinal lesion with delayed healing	Deep tissue abscesses, severe pain, and low mood	Conjunctivitis, painful disruption of thumbnail from subungual lesion	Ulcerated inguinal lesion with delayed healing	None	Pruritus and contact dermatitis from cleaning products	Low mood
Specific management of complications	Clinical psychology input	Empiric broad-spectrum antibiotics, abscess drainage, and analgesia (including opiate and neuropathic drugs)	Antibacterial eye drops	Empiric azithromycin	Nothing specific	Calamine lotion and short course of antibiotics at the onset of dermatitis	Nothing specific
Monkeypox viral DNA detected							
Blood	Yes	Yes	Yes	Yes	No	Yes	Yes
Nose or throat swab	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Urine	Yes	Yes	Yes	Yes	No	No	No

Course or response	2018			2019	2021		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Antivirals received	Brincidofovir 200 mg (1 dose) orally	Brincidofovir 200 mg (2 doses) orally	Brincidofovir 200 mg (2 doses) orally	None	None	None	Tecovirimat 600 mg twice daily for 2 weeks orally
Days of illness before treatment commenced	7	6	7	—	—	—	5
Complications of treatment	Transaminitis (peak ALT 331 U/L)	Transaminitis (peak ALT 550 U/L)	Transaminitis (peak ALT 127 U/L), nausea, and abdominal discomfort	—	—	—	None
Duration of hospitalization with monkeypox, days	26	27	35	39	13	22	10
Outcome of monkeypox infection	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery

ALT = alanine transaminase; HCID = high consequence infectious disease; MVA-BN = modified vaccinia Ankara.

Source: Alder et al.27. Copyright 2022. This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. Original work available here: https://doi.org/10.1016/S1473-3099(22)00228-6.

Monkeypox in a Traveller Returning From Nigeria to Dallas, Texas

Recently, a case report was published involving a traveller with monkeypox who returned from Nigeria to Dallas.[32] This individual travelled to Lagos on June 25, 2021, with prodrome symptoms first appearing on June 30. He attended a large social gathering on July 2, developed rash on July 7, and subsequently took a flight from Lagos to Atlanta, Georgia, on July 8. On July 9, he took a flight from Atlanta, Georgia, to Dallas and was admitted to hospital on July 13. In total, 223 non–high-risk contacts were identified and recommended for monitoring and additional interventions as determined by local public health officials. Thirty-four contacts were recommended to consider ACAM2000 (the orthopoxvirus vaccine) but none of these contacts received the vaccine. The infected traveller received treatment with tecovirimat due to severe disease. He remained in hospital for a total of 32 days and his discharge was delayed to ensure 1 remaining lesion tested negative for monkeypox virus DNA by polymerase chain reaction (PCR) test.

Table 9: A Summary of Cases in Orthopoxvirus Infections Treated With Tecovirimat

Study	Case	Patient history	Route of infection	Tecovirimat and other antiviral treatment details	Outcome
Lederman et al. (2012)[25,33]	Progressive vaccinia	US Marine Corps member with unknown myelogenous leukemia	Primary transmission via smallpox vaccination	VIG IV: 6,000 IU/kg, 18,000 IU/kg, 24,000 IU/kg Tecovirimat topical Tecovirimat oral, escalating dose: 400 mg to 800 mg to 1,200 mg	Discharged 5 months after vaccination with ACAM2000
CDC (2009)[34]	Vaccinia infection of the hand	35-year-old female taking immunosuppressive medications for IBD	Primary transmission via contact with raccoon rabies vaccine bait	VIG IV: 2 doses given at 6000 IU/kg Tecovirimat: unknown dose for 14 days	Discharged after 19 days; lesions healed 22 days after first dose of VIG IV and 16 days after tecovirimat
Vora et al. (2008)[35]	Eczema vaccinatum	28-month baby with history of refractory atopic dermatitis and failure to thrive	Secondary transmission via contact military smallpox vaccinee (father)	VIG IV: 3.96 g/kg in 11 doses CDV: 1 dose 5 mg/kg Tecovirimat: 5 mg/kg for 14 days Trifluridine: unknown	Discharged 48 days after hospitalization
Adler et al (2022)[27]	Monkeypox case in UK	A female between 30 and 40 years developed symptoms while caring for her child in the hospital who also had monkeypox	Tertiary transmission via contact with child	Tecovirimat 600 mg twice daily for 2 weeks	Full recovery
CDC (2022)[32]	Monkeypox in a traveller from Nigeria	A middle-aged man who returned from Nigeria	Transmission from unknown source	Tecovirimat with unknown dose for 2 weeks	Full recovery with discharge after 32 days
Sacks et al. (2021)[36]	Orbital cowpox	A 28-year-old female presented with ocular symptoms, including worsening redness, irritation, and discharge in the right eye	Secondary transmission via contact of pet cat that developed lesions on the paws and head, with PCR test confirmation for orthopoxvirus	Prolonged course of tecovirimat Oral prednisolone Topical dexamethasone Topical moxifloxacin	6 months later, visual acuity was 20/20 with mild residual ptosis and restriction of extraocular movement

CDV = cidofovir; IBD = inflammatory bowel disease; VIG IV = vaccinia immunoglobulins IV; PCR = polymerase chain reaction.

Potential Concerns With Drug Resistance

Drug resistance has been reported for cidofovir.[25] To date, there are no known naturally occurring orthopoxviruses resistant to tecovirimat.[3,29] However, this can theoretically occur under drug selection. Amino acid substitutions and insertions in the VP37 proteins have been noted in the tecovirimat isolates cowpox virus, vaccinia virus, and camelpox virus isolated under drug selection.[29]

The possibility of resistance to tecovirimat should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness. At least 1 case report has been published that describes the development of resistance to tecovirimat following extended systemic treatment at subtherapeutic plasma levels, along with concurrent topical tecovirimat application.[33]

There have been reports of using tecovirimat with brincidofovir as the combination, which may allow for synergistic effects while minimizing resistance development.[25] In this systematic review, 2 animal studies were identified to examine the coadministration of brincidofovir and tecovirimat, in a lethal dose model. In various dose combinations, brincidofovir and tecovirimat were able to achieve high levels of protection, whereas monotherapy did not.[25] As the evidence was derived from animal studies, future research is needed to delineate how to best minimize tecovirimat resistance, in the context of treating orthopoxvirus infections, and tolerability in human patients for whom brincidofovir has caused significant side effects.

Tecovirimat Use in Post-Exposure Prophylaxis

While the focus of this review was tecovirimat for the treatment of monkeypox infection, it is important to be aware of ongoing clinical studies that may provide evidence for an expanded role of tecovirimat in PEP. Currently, treatment may be delayed due to confirmation of diagnosis via PCR test results.

In addition, there has been evidence via animal studies that the combination use of vaccine and antivirals may improve and/or extend the efficacy of post-exposure vaccination.[37]

There is currently an active study looking at the use of the MVA-BN vaccine with or without tecovirimat to evaluate the safety and pharmacokinetics of tecovirimat as well as the impact of tecovirimat on the MVA-BN vaccine's immunogenicity. The studied dose of tecovirimat is 600 mg twice daily for 28 days and the primary outcomes are GMT (geometric mean titer) of vaccinia virus–neutralizing antibodies on day 29 and day 43.[38]

Critical Appraisal

Given the ethical concerns with evaluating tecovirimat in human subjects for orthopoxvirus infections, there have only been animal studies that demonstrated the efficacy of tecovirimat. This is in accordance with the requirements of the FDA Animal Rule for drug development and approval process. Given that the model for approval was

for a more highly lethal pathogen, external validity with monkeypox is not guaranteed. While there does appear to be antiviral effect, the clinical benefits in terms of patient-important outcomes require more study before definitive statements about efficacy in monkeypox can be made.

As such, human clinical evidence of tecovirimat can only be inferred from case reports. Among the 3 case reports describing the use of tecovirimat for vaccinia infections, all patients were co-administered with other treatment interventions, including vaccinia immunoglobulins IV and/or antivirals, including cidofovir and brincidofovir. Given these competing exposures, the case reports primarily provide results that tecovirimat is well tolerated.

As for the 1 observational study describing the experience of tecovirimat in human monkeypox, it is difficult to draw any conclusion as only 1 patient in the study was exposed to tecovirimat. In addition, it is uncertain if earlier administration of tecovirimat on day 5 versus administration of brincidofovir on days 6 or 7 contributed to improved outcome.

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Appendix 1: Animal Studies With Tecovirimat

Table 10: Key Animal Studies With Tecovirimat

Author, reference	Study keypoints and/or abstract	Population	Intervention and comparator	Outcome
Berhanu A et al.[39] Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. *Antimicrob Agents Chemother.* 2015;59(7):4296-4300.	The therapeutic efficacies of smallpox vaccine (ACAM2000) and antiviral tecovirimat given alone or in combination starting on day 3 postinfection were compared in a cynomolgus macaque model of lethal monkeypox virus infection. Postexposure administration of ACAM2000 alone did not provide any protection against severe monkeypox disease or mortality. In contrast, postexposure treatment with tecovirimat alone or in combination with ACAM2000 provided full protection. Additionally, tecoviroimat treatment delayed until day 4, 5 or 6 post infection was 83% (days 4 and 5) or 50% (day 6) effective.	Cynomolgus macaque model	With or without ACAM2000	Postexposure treatment at day 3 provide full protection
Smith, Scott K et al. Poxvirus Team[40] Smith SK, Olson VA, Karem KL, Jordan R, Hruby DE, Damon IK. In vitro efficacy of ST246 against smallpox and monkeypox. *Antimicrob Agents Chemother.* 2009;53(3):1007-1012.	In Vitro Efficacy of ST 246 against Smallpox and Monkeypox	N/A	In vitro efficacy study	Support ST-246 as an alternative for treating orthopoxvirus infections
Stabenow J et al.[41] Stabenow J, Buller RM, Schriewer J, West C, Sagartz JE, Parker S. A mouse model of lethal infection for evaluating prophylactics and therapeutics against Monkeypox virus. *J Virol.* 2010;84(8):3909-3920.	Here we report that a relatively low-dose intranasal (IN) infection induces 100% mortality in the stat1 model by day 10 postinfection with high infectious titers in the livers, spleens and lungs of moribund animals. Vaccination with modified vaccinia virus Ankara (MVA) followed by a booster vaccination is sufficient to protect against an intranasal MPXV challenge and induces an immune response more robust than that of a single vaccination. Furthermore, antiviral treatment	Moribund animal	Vaccine + Cidofovir / ST-246	Cidofovir and ST-246 protects when administered on day of infection

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	with CMX001 (HDP-cidofovir) and ST-246 protects when administered as a regimen initiated on the day of infection. Thus, the Stat1 model provides a lethal murine platform for evaluating thearpeutics and for investigating the immunological and pathological response to MPXV infection.			
Sbrana E et al.[42] Sbrana E, Jordan R, Hruby DE, et al. Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection. *Am J Trop Med Hyg.* 2007;76(4):768-773.	Efficacy of the new antipoxvirus compound ST-246 was evaluated as treatment of monkeypox (MPX) virus infection in a ground squirrel model of the disease. Ground squirrels were given a lethal dose of MPX virus and were then treated orally at various times post-inoculation (pi) with 100mg/kg/day of ST-246. Morbidity and mortality, clinical laboratory results, viral load, and pathology of placebo and treatment groups were compared. All animals that started treatment with ST-246 on days 0, 1, 2 and 3 pi survived lethal challenge with MPX virus; 67% of animals treated on day 4 pi also survived. In contrast, 100% of the placebo group died. Most of the ST-246 treated animals showed no evidence of clinical disease or alteration of baseline clinical laboratory values and had minimal histopathologic changes. These results suggest that ST-246 is a promising candidate for early treatment of severe orthopoxvirus infection.	Ground squirrel model	Placebo controlled	ST-246 treated animals showed no evidence of clinical disease.

Note: ST-246 is tecovirimat.