Tecovirimat Guidance

Refer to Summary of Product Characteristics (SmPCs) of Tecovirimat for full prescribing information

Drug Name	Tecovirimat SIGA
Mechanism of action	Tecovirimat inhibits p37, a protein that is present and highly conserved (approximately 98% amino acid identity) in all orthopoxviruses; the inhibition of p37 prevents the formation and egress of enveloped virions, which are essential for virulence [1].
Background	*Clinical features* The current outbreak of Mpox[1] in Europe, America and other regions is mainly affecting gay, bisexual and other men who have sex with men. It is presenting with lesions on skin and mucosal areas and is often accompanied by other symptoms such as headache, fever, myalgia and lethargy. The largest observational cohort reported during this current outbreak provides data on 528 Mpox cases [2]. 13% required hospitalisation for reasons such as pain management and bacterial super-infection. 5% of people received antiviral treatment: intravenous or topical cidofovir (2%), tecovirimat (2%) and immunoglobulin (<1%). As of August 2022, two deaths have been reported in mainland Europe associated with this specific outbreak. *Evidence on efficacy of Tecovirimat* Efficacy of tecovirimat has been studied in rabbits and non-human primates, demonstrating that tecovirimat prevented death in 80 to 100% of animals when administered up to and including 5 days post Mpox infection [3]. This survival rate reduced to 50% when treatment was initiated 6 days after infection. *Evidence on safety* Phase 2 studies of tecovirimat in healthy human volunteers have demonstrated safety. One randomized controlled trial of 107 healthy volunteers showed the most common side effects to be nausea and headache [4]. In another phase 2 trial of 30 volunteers, side effects were only experienced at the highest dose tested and included GI upset, dry mouth and headache [5]. Although one human study with 40 patients recorded two instances of neutropaenia, these were not thought to be drug related [6]. The largest trial to assess safety in humans recruited 449 healthy volunteers and assigned 361 to tecovirimat at a dose of 600mg twice daily for 14 days. 1.1% experience at least a grade 3 side effect, with headache being the most common symptom [3]. Pharmaceutical data highlights two drug interactions namely a risk of hypoglycaemia when tecovirimat is co-administered with repaglinide and a decrease in midazolam effectiveness [7].
Clinical prioritisation	Tecovirimat should only be initiated following discussion with an ID or GUM consultant in a tertiary centre accustomed to managing these patients.

[1] Formerly referred to as Monkeypox. Replacement of the name Monkeypox with the synonym Mpox was recommended by the World Health Organisation in November 2022, https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease#:~:text=Following%20a%20series%20of%20consultations,%E2%80%9Cmonkeypox%E2%80%9D%20is%20phased%20out.

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Tecovirimat should be considered in patients who have evidence of severe disease <u>or</u> are in a high risk group

Severe disease:

- Haemorrhagic disease, confluent lesions, encephalitis, pneumonitis
- Eye Disease
- Numerous Lesions (> 100)
- Severe local disease
- Other conditions requiring hospitalisation excluding admission for isolation purposes only

High Risk Groups

- Immunocompromised **
- Paediatric especially < 12 years
- Pregnancy/Breast Feeding
- Atopic Dermatitis or other skin disease

Where supply is limited tecovirimat should be used according to priority group order [8].

<table>
<tr><td>Highest Priority</td><td>Life threatening disease (encephalitis, pneumonitis)

Eye disease

Numerous lesions (>100) in immune compromised or children <12 years old</td></tr>
<tr><td>Middle Priority</td><td>Numerous lesions(>100) in all other patients

Severe local disease in immunocompromised or <12 years old</td></tr>
<tr><td>Lower Priority</td><td>Severe local disease general population</td></tr>
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**Immunocompromising conditions e.g. HIV/AIDS (detectable VL and/or CD4<200), Leukaemia, Lymphoma, Generalised malignancy, solid organ transplantation, recent chemotherapy/immunotherapy/high dose steroids, Haematopoietic stem cell transplant recipient, autoimmune disease with immunodeficiency as clinical component.
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<td>Pregnancy Recommendations</td>
<td>Pregnant women may be more vulnerable to the adverse effects of Mpox and liable to more severe symptoms as well as risks to the fetus. Pregnant women are a risk group that should be considered for Tecovirimat following a risk benefit discussion. The decision to treat should involve Maternal- Fetal medicine consultation.</td>
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<td>Paediatric Recommendations</td>
<td>Data from previous outbreaks suggest that the risk of severe disease with Mpox infection is increased in children, particularly in the first year of life. Tecovirimat is authorised for use in children weighing over 13kg but its use should be considered in smaller children as these are the most at risk group. All children with Mpox infection should be discussed with the Paediatric Infectious Disease service in Children’s Health Ireland.</td>
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<tr><td>Formulation</td><td>Tecovirimat SIGA 200 mg hard capsules; each hard capsule contains tecovirimat monohydrate equivalent to 200 mg tecovirimat. In time, intravenous formulation may become available in Ireland and guidance will be updated at that time.</td></tr>
<tr><td>Route of Administration</td><td>Oral use only</td></tr>
<tr><td>Dose & Duration of Therapy [7,9,10]</td><td>Tecovirimat treatment should be initiated as soon as possible after diagnosis.

Adults (≥ 40 kg): 600 mg Twice Daily for 14 days (Three 200 mg capsules per dose).

Children (≥ 13 kg): The recommended doses by bodyweight are:
<table>
<tr><th>Body Weight</th><th>Dosage</th><th>Number of Capsules</th></tr>
<tr><td>≥ 13 kg - < 25 kg</td><td>200 mg Twice Daily for 14 days</td><td>One 200 mg capsule per dose</td></tr>
<tr><td>≥ 25 kg - < 40 kg</td><td>400 mg Twice Daily for 14 days</td><td>Two 200 mg capsule per dose</td></tr>
<tr><td>≥ 40 kg</td><td>600 mg Twice Daily for 14 days</td><td>Three 200 mg capsules per dose</td></tr>
</table>
Renal Impairment: No dose adjustment required but use with caution in patients with severe renal impairment.
Hepatic Impairment: No dose adjustment required but use with caution in patients with severe hepatic impairment.

Re-dosing if Vomiting Occurs:
▪ If vomiting occurs within 30 minutes of taking tecovirimat - administer another dose immediately.
▪ If vomiting occurs more than 30 minutes after taking tecovirimat - no additional dose should be given & dosing should resume as usual after 12 hours.</td></tr>
<tr><td>Method of Administration</td><td>Tecovirimat should be taken within 30 minutes of a moderateorhighfatmeal (approx. 600 calories & 25 g fat).

If patient unable to swallow: The capsules may be opened and the contents mixed with 30 mL of liquid (e.g. milk) or soft food (e.g. yogurt). This mixture should be taken within 30 minutes of preparation and within 30 minutes of a moderateorhighfatmeal (approx. 600 calories & 25 g fat).
Refer to https://www.cdc.gov/poxvirus/Mpox/pdf/Attachment-3-Opening-Capsules-Mixing-with-Food.pdf for further guidance on administering to patients unable to swallow.</td></tr>
<tr><td>Drug – Drug Interactions</td><td>▪ Clinically significant drug interactions are not expected for most co-administered drugs.
▪ Tecovirimat & its M4 metabolite are inducers of CYP3A and CYP2B6.
▪ Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19.
▪ Monitoring is advised during co-administration with CYP3A4 / CYP2B6 / CYP2C8 / CYP2C19 substrates that have narrow therapeutic windows (Examples include Midazolam, Voriconazole, Tacrolimus)

Refer to drug interaction resources on how to minimise these drug interactions:
▪ Tecovirimat SmPC</td></tr>
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	▪ eBNF Interactions ▪ Lexicomp (Uptodate) ▪ HSE Antibiotic Prescribing Drug Interactions ▪ Liverpool Drug Interaction Checkers ▪ Toronto HIV / HCV Therapy Guide
Adverse Effects	▪ Headache ▪ Nausea ▪ Abdominal pain / discomfort ▪ Diarrhoea / Vomiting ▪ Dizziness

References:

1. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, Lovejoy C, Meara I, Long P, Hruby DE. N Engl J Med. 2018 Jul 5;379(1):44-53. doi: 10.1056/NEJMoa1705688. PMID: 29972742. OralTecovirimat for theTreatmentofSmallpox.
2. Thornhill, J.P., et al., *Mpox Virus Infection in Humans across 16 Countries - April-June 2022.* N Engl J Med, 2022.
3. Grosenbach, D.W., et al., *Oral Tecovirimat for the Treatment of Smallpox.* N Engl J Med, 2018. 379(1): p. 44-53.
4. Chinsangaram, J., et al., *Safety and pharmacokinetics of the anti-orthopoxvirus compound ST-246 following a single daily oral dose for 14 days in human volunteers.* Antimicrob Agents Chemother, 2012. 56(9): p. 4900-5.
5. Jordan, R., et al., *Safety and pharmacokinetics of the antiorthopoxvirus compound ST-246 following repeat oral dosing in healthy adult subjects.* Antimicrob Agents Chemother, 2010. 54(6): p. 2560-6.
6. Jordan, R., et al., *Single-dose safety and pharmacokinetics of ST-246, a novel orthopoxvirus egress inhibitor.* Antimicrob Agents Chemother, 2008. 52(5): p. 1721-7.
7. Summary of Product Characteristics for Tecovirimat SIGA 200 mg hard capsules, SIGA Technologies Netherlands B.V. (EU/1/21/1600/001). First published: 28/01/2022. Available from: https://www.ema.europa.eu/en/documents/product-information/tecovirimat-siga-epar-product-information_en.pdf (Accessed 25/7/2022)
8. UK HCID network [personal communication]
9. Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Mpox Cases. Updated: 15 July 2022. Available from: https://www.cdc.gov/poxvirus/Mpox/clinicians/Tecovirimat.html (Accessed 26/07/2022)
10. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children. Version 6, 20 July 2022. Available from: https://www.cdc.gov/poxvirus/Mpox/pdf/Tecovirimat-IND-Protocol-CDC-IRB.pdf (Accessed 26/07/2022)
11. WHO *Mpox Fact Sheet*. 2022.
12. ECDC *Mpox multi-country outbreak*. 23rd May 2022.

Appendix

Table 1. International guidelines on clinical indications for Tecovirimat treatment of Mpox and suggested prioritisation.

Source	Prioritisation groups
WHO [11] **July 2022**	Should be given within clinical trial setting
CDC [9] **July 2022**	**1.** Severe disease (haemorrhagic disease, confluent lesions, sepsis, encephalitis or other conditions requiring hospitalisation) **2.** High risk groups - Immune compromised - Paediatric esp. < 12 years - Pregnancy/Breast feeding - Atopic Dermatitis or other skin disease - Complication (secondary skin infection, gastroenteritis, bronchopneumonia, concurrent disease with other comorbidities) **3.** Aberrant infections involving eyes, mouth, genitals, anus or other areas that may present a special hazard.
ECDC [12]	Clinicians and infectious diseases societies need to provide guidance for use
UK HCID network [8] **[personal communication]**	**1. High priority** - **L**ife threatening disease (encephalitis, pneumonitis) - Eye disease - Numerous lesions (>100) in immune compromised or children <12 years old **2. Middle priority** - Numerous lesions(>100) in all other patients - Severe local disease in immunocompromised or <12 years old **3. Lower priority** - Severe local disease general population