Evidence summary
Antiviral treatment options for human monkeypox infection

This document is intended for use by NHS healthcare professionals as a quick reference guide to the three potential antiviral treatment options for human monkeypox infection. Members of the public may need assistance to interpret the information and translate it to their own situation; it is strongly recommended to seek relevant professional advice in such cases. The information provided is believed to be an accurate reflection of the medical literature at the time of preparation. However, users should consult the literature and take account of new developments.

	Tecovirimat	Brincidofovir	Cidofovir
Licence status	Licensed by the European Medicines Agency (EMA) for the treatment of smallpox, monkeypox and cowpox in adults and children weighing at least 13 kg. (1) Approved by the Food and Drug Administration (FDA) for the treatment of human smallpox disease. (2,3)	Approved by the FDA for the treatment of human smallpox in adult and paediatric patients, including neonates. (11) Granted orphan drug designation by the EMA for the treatment of adenovirus infection in immunocompromised patients, the treatment of smallpox and prevention of cytomegalovirus disease. (12,13)	Licensed in the UK for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immune deficiency syndrome (AIDS) without renal dysfunction. (18)
Efficacy data	Tecovirimat has been shown to treat non-human primates infected with monkeypox virus successfully. (4-6) One study reported a 100% survival when the medication was initiated on days 1-5 and day 7 post-infection, and a 66% and 50% survival when initiated on day 6 and day 8, respectively. (6) One patient with monkeypox was treated with tecovirimat 600 mg BD for 14 days, initiated 5 days after their illness started. (7) The patient experienced a shorter duration of symptoms and upper respiratory tract viral shedding than those untreated or treated with brincidofovir; it is unclear if this is due to tecovirimat. (7) Another patient was also treated with tecovirimat in Texas 2021; no details regarding their progress are provided. (8)	Brincidofovir has shown an increased survival trend in treating prairie dogs infected with monkeypox virus, with more animals surviving the sooner brincidofovir was initiated. (14) A 29% survival rate was observed when initiated on day 1 post-infection compared to 14% in control animals. (14) There was no statistically significant survival difference between the treatment and control groups. (14) Three patients with monkeypox were treated with oral brincidofovir commenced approximately 7 days post-onset of the rash. (8) Brincidofovir was not observed to provide any convincing clinical benefit in any of the patients, although treatment was discontinued early in all patients due to raised liver enzymes. (8) Transient reductions were seen in viral loads, but these improvements were not durable or consistent between patients. (8)	Cidofovir has shown *in vitro* activity against monkeypox virus. (19) Cidofovir 5 mg/kg intravenously has been reported to successfully treat monkeypox in monkeys when given prior to infection or up to 2 days post-infection. (20,21) Treatment led to complete protection with no signs of illness and control of viral replication in blood. (20,21) The referenced studies are review articles that refer to abstracts with unpublished data. Cidofovir 5 mg/kg intraperitoneally has successfully treated monkeys infected with monkeypox when initiated 24 hours after infection. (22) Animals that received treatment had significantly lower plasma viral loads than the control group. (22) No reports of cidofovir used to treat monkeypox virus in humans have been identified.

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Safety data	The most frequently reported adverse effects include headache (12.3%) and nausea (4.5%). (1) Common adverse effects (≥1/100 to <1/10) include dizziness, abdominal pain, upper abdominal discomfort, diarrhoea and vomiting. (1) In a safety trial, 361 healthy human volunteers received 600 mg BD for 14 days. (9) Severe adverse effects (grade 3 or higher) occurred at a similar frequency to placebo (1.1% in both groups). (9)	In clinical trials experience, diarrhoea, nausea, vomiting, and abdominal pain occurred in >2% of patients; treatment had to be discontinued due to some of these effects. (11) Additional effects that led to treatment discontinuation were vomiting, enteritis, increased ALT, and dyspepsia. (11) Adverse reactions that occurred in <2% of patients include peripheral oedema, decreased appetite, muscular weakness, dysgeusia and a rash. (11) In 392 patients administered with brincidofovir, ALT elevations >3x the upper limit of normal were reported in 7% of subjects and bilirubin elevations >2x the upper limit of normal were reported in 2% of subjects. (11) These elevations were generally reversible and did not require discontinuation of therapy. (11) Elevated AST levels have also been reported. LFTs should be monitored before starting therapy and while receiving as clinically appropriate. (11) In a recent retrospective observational study, all three patients treated with brincidofovir developed deranged liver enzymes resulting in discontinuation of treatment. (8) Treatment was discontinued after one dose in one patient and after two doses in the remaining two patients. (8) The patients had peak ALT readings of 331, 550 and 127 U/L, respectively. (8) In a phase 3 trial, 100 mg twice weekly was administered for up to 14 weeks to prevent cytomegalovirus, all-cause mortality at week 24 was 16% in the treatment group and 10% in the placebo group. (11) Due to this, brincidofovir is not indicated for use in other diseases other than smallpox at the licensed dose. (11) Brincidofovir is considered a potential carcinogen, therefore, direct contact with broken or crushed tablets or oral suspension should be avoided. (11)	Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to the administration of cidofovir. (18,23) Cases of acute renal failure have been reported after only one or two doses of cidofovir. (18) Patients must have their serum creatinine and urine protein levels sampled within 24 hours prior to administering each dose. (18) Cidofovir should be discontinued if serum creatinine increases by ≥44 µmol/l, or if persistent proteinuria ≥2+ develops. (18) To minimise potential nephrotoxicity, oral probenecid and IV saline pre-hydration must be administered with each dose (see dosing below). (18) White blood cell counts should also be performed before each dose due to the risk of neutropenia. (18) Patients receiving cidofovir for CMV retinitis should have regular follow-up ophthalmologic examinations due to the possibility of uveitis/iritis and ocular hypotony. (18) Very common (≥1/10) side effects include neutropenia, headache, nausea, vomiting, alopecia, rash, proteinuria, blood creatinine increases, asthenia, and fever. (18) Common side effects (≥1/100 to <1/10) include iritis, uveitis, hypotony of the eye, dyspnoea, diarrhoea, renal failure, and chills. (18) An uncommon side effect (≥1/1000 to <1/100) includes Fanconi syndrome; any finding of glycosuria, proteinuria, hypouricemia, hypophosphatemia and/or hypokalaemia should prompt consideration of cidofovir-related Fanconi syndrome. (18) Probenecid (which must be administered with cidofovir) must be administered with cidofovir which can cause headache, nausea, vomiting, rash, fever, asthenia and chills. (18)

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		In 23 paediatric subjects aged 7 months to 17 years, the adverse reactions and laboratory abnormalities observed with brincidofovir were similar to adults. (11) Brincidofovir may have an improved safety profile over cidofovir. (15) Serious renal toxicity has not been observed during treatment compared to cidofovir. (15)	Cidofovir should be reconstituted in a laminar flow biological safety cabinet with appropriate PPE and should be considered a potential carcinogen. (18)
Dosing – adults	**Body weight 13kg to <25kg:** 200 mg every 12 hours for 14 days (1,3) **Body weight 25kg to <40kg:** 400 mg every 12 hours for 14 days (1,3) **Body weight 40kg and above:** 600 mg every 12 hours for 14 days (1,3)	When used for smallpox: (11,16) **Body weight <10kg:** 6 mg/kg once weekly for 2 doses (day 1 and day 8) **Body weight 10kg to <48kg:** 4 mg/kg once weekly for 2 doses (day 1 and day 8) **Body weight 48kg and above:** 200 mg once weekly for 2 doses (day 1 and day 8) A dose of 200 mg once weekly for 3 doses was selected in a recent retrospective observational study to treat human monkeypox following a discussion with the manufacturer. (8)	For CMV retinitis, a dose of 5mg/kg intravenously is recommended, administered once weekly for two consecutive weeks, followed by a maintenance dose of 5 mg/kg once every two weeks. (18) 2g of oral probenecid should be administered 3 hours before the cidofovir dose and 1g administered at 2 hours and 8 hours post-dose (for a total of 4g). (18,24,25) Pre-hydration with 1 litre of sodium chloride 0.9% should be administered intravenously prior to each cidofovir infusion. (18,24,25) If patients can tolerate additional fluid, a second 1 litre infusion of sodium chloride 0.9% should be administered simultaneously with the cidofovir dose or immediately after the dose. (18,24,25)
Dosing – children	See above Tecovirimat should not be administered to children <13 kg body weight. (1) No dose recommendations have been established. (1)	See above	The safety and efficacy of cidofovir in children below 18 years of age has not been established and is therefore not recommended. (18,24)
Formulations	200 mg hard capsules. (1) Capsules should be taken within 30 minutes after a moderate or high fat meal. (1) Capsules may be opened and the contents mixed with 30 mL of liquid or soft food. (1)	100 mg tablets and 10 mg/mL oral suspension. (11) Tablets should be taken whole on an empty stomach or with a low-fat meal (approximately 400 calories, with approximately 25% of calories from fat). (11) Oral suspension should be taken on an empty stomach and can be administered via a nasogastric or gastrostomy tube. (11)	75 mg/mL concentrate for intravenous infusion. (18)

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Dosing – renal impairment	No dose adjustment is necessary for mild, moderate, or severe renal impairment or in patients receiving haemodialysis. (1,3) Caution in severe renal impairment due to limited clinical data. (1)	No dose adjustment is required for patients with mild, moderate, or severe renal impairment or patients with end-stage renal disease (ESRD) receiving dialysis. (11,16,17)	Contraindicated if creatinine clearance ≤55 mL/min or ≥2+ proteinuria (≥100 mg/dL). (18) The manufacturer and renal drug database recommend dosing as in normal renal function with a creatinine clearance >55 mL/min. (18,26) In the USA, a reduction in the maintenance dose from 5 mg/kg to 3 mg/kg is recommended for increases in serum creatinine of 300 to 400 micrograms/dL. (25)
Dosing – hepatic impairment	No dose adjustment is necessary for mild, moderate or severe hepatic impairment. (1,3) Caution in severe hepatic impairment due to limited clinical data. (1,3)	**Hepatic impairment prior to treatment:** no dosage adjustment necessary for mild, moderate, or severe impairment (Child-Pugh A, B, or C) (11,16,17) **Hepatic impairment during treatment:** consider discontinuation if ALT levels remain >10x the upper limit of normal. Do not administer the second (final) dose on day 8 if ALT elevation is accompanied by clinical signs and symptoms of liver inflammation or increasing bilirubin, ALP, or INR. (11,17)	The safety and efficacy of cidofovir has not been established in patients with hepatic disease, and therefore should be used with caution. (18,27)
Drug interactions	Tecovirimat and its metabolites are inducers of CYP3A4 and CYP2B6. (1,10) Examples of possibly reduced serum concentrations include carbamazepine, clozapine, phenytoin, hormonal contraceptives, atorvastatin, methadone, sirolimus and tacrolimus. (1,10) Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19. (1,10) Examples of possibly increased serum concentrations include proton pump inhibitors and repaglinide. (1,10)	Brincidofovir is a direct and reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP4F2. (11) Brincidofovir is an inhibitor of OATP1B1, OAT1, OAT3 Breast Cancer Resistance Protein (BCRP) and multidrug resistance-associated protein 2 (MRP2). (11) Concomitant use of OATP1B1 and 1B3 inhibitors may increase brincidofovir concentrations. (11) Examples include clarithromycin, ciclosporin, erythromycin, gemfibrozil, protease inhibitors, rifampicin. (11) Corticosteroids, immunosuppressants (cytotoxic chemotherapy, therapeutic immunosuppressant agents) and methotrexate may diminish the therapeutic effect of brincidofovir. (17) Brincidofovir should not be co-administered with intravenous cidofovir. (11)	Potentially nephrotoxic medication should be discontinued at least 7 days before starting therapy. (18) Examples of nephrotoxic medication include aminoglycoside, amphotericin B, pentamidine, and vancomycin. (18,24) Administration of tenofovir disoproxil with cidofovir should be avoided due to the risk of Fanconi syndrome. (18) Probenecid is known to increase the exposure to many substances, including paracetamol, acyclovir, ACE inhibitors, aspirin, barbiturates, benzodiazepines, bumetanide, methotrexate, furosemide, NSAIDs, theophylline and zidovudine. (18,25)

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Use in pregnancy	There are insufficient data using tecovirimat in pregnant women. (1,3) Treatment is therefore not recommended during pregnancy. (1,3) Maternal toxicity was not observed in pregnant mice that received doses up to 23 times the recommended human dose. (3) Male mice developed testicular toxicity, including an increase in abnormal sperm and decreased sperm motility. (3) The effects of tecovirimat on fertility in humans has not been studied. (3)	Brincidofovir caused foetal harm to animal models at systemic exposures less than the expected human exposure. (11,16) The manufacturer advises using an alternative therapy when used to treat smallpox. (11) Patients of childbearing potential should undergo pregnancy testing before initiation. Patients should be advised to avoid becoming pregnant and to use effective contraception during treatment for at least two months after the last dose. (11) Male patients with partners of childbearing potential should be advised to use condoms during treatment and for at least four months after the last dose. (11) Based on testicular toxicity in animal studies, brincidofovir may irreversibly impair fertility in those of reproductive potential. (11,16)	Not recommended during pregnancy and in women of childbearing potential not using contraception. (18) Studies in animals have shown reproductive toxicity. (18) As cidofovir is potentially genotoxic, women of childbearing potential should use effective contraception while being treated with cidofovir and for six months following completion. (18) Men are recommended to use effective contraception and not father a child whilst being treated and for three months following completion. (18)
Use in breastfeeding	It is unknown whether tecovirimat and its metabolites are excreted into human milk. (1,3) Available data in animals has shown excretion into milk. A risk to the infant cannot be excluded. The manufacturer advises that breastfeeding should be discontinued during treatment. (1)	There are no data on the presence of brincidofovir in human milk, the effects of the drug on the breastfed infant or on milk production. (11,16) When brincidofovir was administered to lactating rats, the medication was detected in milk but not in the plasma of nursing pups. (11,16)	It is not known if cidofovir is present in breast milk, therefore a risk to neonates/infants cannot be excluded. (18,24) Breastfeeding should be discontinued during treatment with cidofovir. (18)

Limitations:

Consult the Summary of Product Characteristics before prescribing, including probenecid if using cidofovir. Data regarding the use of tecovirimat and brincidofovir in humans to treat monkeypox is from retrospective observational case studies. No information regarding the use of cidofovir to treat monkeypox virus has been identified. Information regarding intravenous cidofovir to treat monkeypox virus in non-human primates is from review articles that reference conference abstracts with unpublished data.

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