# Oseltamivir for influenza

## Intervention

Oseltamivir 75mg twice daily for 5 days, given by mouth or nasogastric tube. Complete the course at home if discharged.

Treat for 10 days if the patient is immunosuppressed in the opinion of the managing clinician. Dose adjustment is needed in renal impairment or weight <40kg, as below.

## Information on oseltamivir for influenza

Neuraminidase inhibitors (NAIs), such as oseltamivir and zanamivir, are influenza specific antivirals that prevent budding of the virus from infected cells, inhibiting viral replication. They have been shown to shorten the duration of symptoms of uncomplicated influenza by around one day if given within the first 48 hours of symptoms, but they have not been shown to be effective in patients hospitalised with influenza.[1] Although some observational studies have suggested a benefit in hospitalised patients, others have not, and evidence from randomised trials is lacking.[1,2] During the COVID-19 pandemic, treatments that showed similar promise in observational studies were found to be ineffective in randomised trials.[3,4]

An expert group convened by the Academy of Medical Sciences and the Wellcome Trust concluded that a randomised trial of NAIs in patients hospitalised with influenza was a high priority.[5] A subsequent survey of senior clinicians treating such patients found that use of NAIs in hospitalised patients was very variable.[6] Most did not believe NAIs were effective at reducing mortality in these patients, and the large majority were in favour of a randomised trial.

## Eligibility

- Hospitalised patients with an acute pneumonia syndrome, in general based on:
  a) typical symptoms of new respiratory infection, and
  b) objective evidence of acute lung disease, (e.g. compatible imaging [plain X-ray, CT or ultrasound], clinical examination, or new hypoxia), and
  c) alternative causes considered unlikely
- Confirmed influenza A or B infection (laboratory test or point-of-care test if performed by a healthcare worker).

## Exclusions

- Use of an NAI during the current illness.
- Indication for an NAI, as determined by the patient's managing clinician.
- Contraindication to an NAI as determined by the managing clinician (including hypersensitivity to oseltamivir or product excipients).

## Frequently asked questions

1. ***Can patients receive an NAI if they allocated to the 'usual care' arm?***
   'Usual care' in the oseltamivir comparison means usual care *without* an NAI. Patients who are expected to receive an NAI regardless of trial allocation should *not* be enrolled in this comparison (but they may still be eligible for other RECOVERY comparisons).

If, after randomisation, the managing clinician decides that a patient allocated usual care needs to receive an NAI, then they should do what is best for the patient even if this means departing from the trial allocation.

2. ***Is it acceptable for patients allocated 'usual care' in RECOVERY not to receive an NAI if local/national guidelines recommend it?***
   Treatment guidelines for hospitalised patient must currently rely on results from observational studies, which may be inaccurate.[5] The UK government recommends NAI treatment for hospitalised patients but recognises that evidence to support this is currently inadequate, and so encourages participation in randomised trials when possible.[7,8]

   If local policy recommends that some or all hospitalized patients should receive an NAI, then a local plan should be made about whether these patients can be considered for the oseltamivir arm of RECOVERY.

3. ***Can patients with hepatic impairment be enrolled?***
   Yes, and no dose adjustment is needed.

4. ***Can patients with renal impairment be enrolled?***
   Yes, but dose adjustment may be needed as follows
   - eGFR 10-29 mL/min/1.73m$^2$: 75mg once daily
   - eGFR <10 mL/min/1.73m$^2$: 75mg as a single dose only

   If renal function changes during treatment then adjust dosing frequency according to current eGFR.

5. ***Can pregnant or breastfeeding women be enrolled?***
   Yes. Oseltamivir is commonly used in pregnant women with no evidence of adverse fetal effects. It is excreted in breast milk at low concentrations that would be subtherapeutic to the infant. Inclusion of pregnant women should be discussed with an obstetric specialist (see protocol appendix 4).

6. ***Can children (age <18) be enrolled?***
   This arm is open to children of any age in the UK (see protocol appendix 3 for dosing). Children are excluded in all other countries.

7. ***Can patients with hospital-acquired influenza be enrolled?***
   Yes, if influenza is thought to be the cause of the patient's pneumonia.

8. ***Can oseltamivir be used concomitantly with other treatments?***
   Yes, no significant drug-drug interactions are recognised.

9. ***Does oseltamivir need weight-based dose adjustment?***
   Yes, for patients weighing ≤40kg the dose is:
   10-15 kg 30 mg twice daily
   >15-23 kg 45 mg twice daily
   >23-40 kg 60 mg twice daily
   If there is co-existent renal impairment then use the dose above at a frequency determined by the patient's renal function.

10. ***Can parenteral routes be used?***
    No

## References


1 Heneghan CJ, Onakpoya I, Jones MA, *et al.* Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess* 2016; **20**: 1–242. PMID 27246259

2 Muthuri SG, Venkatesan S, Myles PR, *et al.* Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med* 2014; **2**: 395–404. PMID 24815805

3 C Arnold Egloff SA, Junglen A, Restivo JS, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. J Clin Invest 2021; 131: e151788. PMID 34464352

4 RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021; **397**: 2049–59. PMID 34000257

5 The Academy of Medical Science. Use of Neuraminidase Inhibitors in Influenza. 2015 https://acmedsci.ac.uk/policy/policy-projects/treating-influenza (accessed Oct 14, 2022).

6 Bradbury N, Nguyen-Van-Tam J, Lim WS. Clinicians' attitude towards a placebo-controlled randomised clinical trial investigating the effect of neuraminidase inhibitors in adults hospitalised with influenza. *BMC Health Serv Res* 2018; **18**: 311. PMID 29716584

7 UKHSA. Influenza: treatment and prophylaxis using anti-viral agents. GOV.UK. 2021; published online Nov. https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents (accessed Dec 9, 2021).

8 Chief Medical Officer letter on influenza trials. https://www.recoverytrial.net/files/cmo-letter-on-trials-of-influenza-antivirals-2023-01-03.pdf.