

Influenza antivirals

A small group of drugs active only against influenza, split between four neuraminidase inhibitors that block the release of new virus particles, one newer drug that blocks viral genome transcription at an earlier step, and two adamantanes that used to work against influenza A but no longer do because circulating strains are now resistant.

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/influenza-antivirals>

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Quick revision

One Liner: Four neuraminidase inhibitors (oseltamivir, zanamivir, peramivir, and - historically - laninamivir) block the enzyme that releases new influenza virions from an infected cell, while baloxavir marboxil works earlier by blocking the viral polymerase's cap-snatching endonuclease; both drug families only help if started within about 48 hours of symptom onset, and the two adamantanes are no longer recommended because of resistance.

1. Oseltamivir (Tamiflu, oral), zanamivir (Relenza, inhaled) and peramivir (Rapivab, IV) are neuraminidase inhibitors: they block the viral neuraminidase enzyme that cleaves sialic acid so newly made virus particles can be released from the infected cell surface. [1][2][3]
2. Baloxavir marboxil (Xofluza) works differently: it inhibits the endonuclease activity of the viral polymerase acidic (PA) protein, blocking the cap-snatching step the virus needs to transcribe its own mRNA, which stops replication earlier in the viral life cycle than a neuraminidase inhibitor does. [4]
3. All four current agents share the same core evidence pattern: benefit is greatest, and treatment is indicated, only when started within 48 hours of symptom onset, in patients with acute uncomplicated influenza A or B. [1][4][5]
4. The oseltamivir-resistance mutation H275Y in the neuraminidase gene became the dominant strain characteristic of circulating 2008 seasonal H1N1 influenza, found in more than 99% of US isolates that year, before that specific strain was later displaced by the 2009 pandemic lineage. [1]
5. Baloxavir resistance arises through PA substitutions at position 38 (commonly I38T), which were detected in treatment-emergent isolates from clinical trials at meaningfully higher frequency in children (about 20-28%) than in adults (about 4.5-11%). [4]
6. The adamantanes amantadine and rimantadine block the influenza A M2 ion channel, but the CDC states plainly that they are not recommended for treatment or chemoprophylaxis because of high levels of resistance among circulating influenza A viruses; neither adamantane works against influenza B at all, because influenza B's M2-equivalent protein is structurally different. [5][6]
7. Zanamivir is inhaled and is specifically not recommended for patients with underlying airway disease such as asthma or COPD because of a risk of serious bronchospasm. [2]
8. Baloxavir's absorption is reduced by polyvalent cations, so it should not be taken with dairy products, calcium-fortified beverages, or polyvalent-cation-containing laxatives or antacids. [4]

Overview

1. Influenza antivirals are narrow-spectrum by design: unlike a broad antibacterial, they act against essentially one virus family, and the evidence supporting all of them rests on the same time-sensitive premise - that blocking a step in the influenza replication cycle only meaningfully shortens illness or prevents transmission when the drug is on board early. Every current label repeats a version of the same instruction: begin treatment within 48 hours of symptom onset in a patient with acute, uncomplicated influenza A or B infection. [1][4][5]
2. Two mechanistically distinct families do the current heavy lifting. The neuraminidase inhibitors - oral oseltamivir, inhaled zanamivir, and intravenous peramivir - block the viral neuraminidase enzyme that a newly assembled virus

particle needs to cut itself free from the sialic acid on the surface of the cell it just infected. Baloxavir marboxil, approved more recently, acts earlier in the cycle: it inhibits the endonuclease activity of the influenza polymerase acidic (PA) protein, the enzyme the virus uses to 'snatch' a cap structure from host mRNA so it can transcribe its own genes. Blocking that cap-snatching step stops the virus before it has made new proteins at all, rather than stopping the finished particle from leaving the cell. [1][2][3][4]

3. A third, older family - the adamantanes amantadine and rimantadine - block the influenza A M2 ion channel and once had a real place in seasonal flu treatment. They no longer do. The CDC states directly that amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of influenza because of high levels of resistance among circulating influenza A viruses, a resistance pattern first documented at scale during the 2005-2006 season and never reversed. Neither adamantane has activity against influenza B at all, because influenza B's equivalent protein is structurally different from the M2 channel the drugs target. The class is retained here for historical and exam purposes, not as a current treatment recommendation. [5][6]

4. Route of administration is a genuine, clinically relevant point of difference within the modern class, not a minor detail. Oseltamivir is oral and can be used from 2 weeks of age for treatment; zanamivir is a dry-powder oral inhalation delivered by a Diskhaler device and is avoided in patients with reactive airway disease; peramivir is given as a single intravenous infusion, which matters for a patient who cannot swallow or inhale reliably; and baloxavir is a single oral dose, an adherence advantage the multi-day regimens do not share. [1][2][3][4]

Classification and drug examples

Intro: The class is best organised by mechanism and target: neuraminidase inhibitors act late in the replication cycle at the point of viral release, the cap-dependent endonuclease inhibitor acts early at the point of viral transcription, and the adamantanes - retained for historical and exam context only - act at viral uncoating and are no longer recommended for use.

1. Name: Neuraminidase inhibitors

1. Note: Block the viral neuraminidase enzyme that cleaves sialic acid, preventing newly assembled influenza virions from being released from the infected cell surface and from each other.

1. Name: Oseltamivir

Tamiflu

1. Route: Oral (capsule or oral suspension)

1. Note: The only member of this class approved for treatment from 2 weeks of age and for prophylaxis from 1 year of age; the drug most affected by the H275Y resistance mutation. [1]

2. Name: Zanamivir

Relenza

2. Route: Oral inhalation (dry powder, Diskhaler)

2. Note: Not recommended in patients with underlying airway disease such as asthma or COPD because of a risk of serious bronchospasm. [2]

3. Name: Peramivir

Rapivab

3. Route: Intravenous, single dose

3. Note: Given as a single IV infusion over a minimum of 15 minutes; efficacy has not been established in patients with influenza serious enough to require hospitalisation. [3] [1][2][3]

2. Name: Cap-dependent endonuclease inhibitor

2. Note: A single-dose oral drug that blocks the influenza polymerase acidic protein's endonuclease activity, stopping viral mRNA transcription rather than viral particle release.

Name: Baloxavir marboxil

Xofluza

Route: Oral, single dose

Note: Approved for treatment and post-exposure prophylaxis in patients 5 years and older per CDC guidance, though the manufacturer label covers ages 12 and older; must be taken apart from dairy products and polyvalent-cation antacids or laxatives. [4][5] [4]

3. Name: Adamantanes (historical, not currently recommended)

3. Note: Block the influenza A M2 ion channel, preventing viral uncoating; retained here because they remain a recognised exam topic and an instructive example of a whole drug class being made obsolete by resistance, not because they are a current treatment option.

1. Name: Amantadine

1. Route: Oral

1. Note: Now used mainly for Parkinson disease; the CDC states it is not recommended for influenza treatment or chemoprophylaxis because of high resistance among circulating influenza A strains, and it has no activity against influenza B. [6][5]

2. Name: Rimantadine

2. Route: Oral

2. Note: Shares amantadine's mechanism and the same current non-recommendation for influenza because of resistance. [5] [5][6]

Mechanism of action

Summary: Influenza's replication cycle offers several druggable steps, and the two currently recommended drug families act on two different ones. Neuraminidase inhibitors act at the very end of the cycle, after new virions have already assembled at the infected cell's surface: the viral neuraminidase enzyme normally cleaves sialic acid residues so a finished virion can detach and go on to infect other cells, and blocking that enzyme leaves virions clumped uselessly at the surface instead of spreading. Baloxavir marboxil acts far earlier, before any new viral protein has been made: after the virus enters a cell and its genome reaches the nucleus, the viral RNA polymerase's PA subunit has to 'snatch' a short capped fragment from a host pre-mRNA to prime its own transcription, and baloxavir's active metabolite, baloxavir acid, blocks the endonuclease that performs that snatching step.

Target: Viral neuraminidase (oseltamivir, zanamivir, peramivir); the polymerase acidic (PA) endonuclease of the viral RNA polymerase complex (baloxavir marboxil); the M2 ion channel of influenza A (adamantanes, not currently recommended)

Cidal Static: Functionally virustatic - these drugs suppress viral replication and spread within an infected host rather than eliminating already-formed virus, which is part of why the time window for starting treatment matters so much

Kill Kinetics: Effect depends entirely on how early in the illness the drug is started; benefit measured in this class is a reduction in the duration of symptoms and, for baloxavir, in the duration of infectious virus shedding, not sterilisation of an established infection

1. Step: 1

1. Title: The virus enters a respiratory epithelial cell and releases its genome

1. Detail: Influenza binds sialic acid receptors on the host cell surface, is endocytosed, and its ribonucleoprotein complexes are released into the cytoplasm and trafficked to the nucleus, where transcription and replication of the segmented RNA genome take place. [4]

2. Step: 2

2. Title: Baloxavir acts here: the viral polymerase needs a capped RNA primer

2. Detail: The viral RNA-dependent RNA polymerase's PA subunit has endonuclease activity that cleaves a short capped fragment from host pre-mRNA (cap-snatching) to use as a primer for viral mRNA synthesis; baloxavir marboxil's active metabolite inhibits this endonuclease, blocking viral mRNA transcription before any new viral protein is made. [4]

3. Step: 3

3. Title: If transcription proceeds, the virus assembles new virions at the cell surface

3. Detail: Newly made viral proteins and genome segments assemble into new virions that bud from the infected cell's plasma membrane, still tethered to the cell surface by sialic acid interactions with the viral haemagglutinin. [1]

4. Step: 4

4. Title: Neuraminidase inhibitors act here: release of the new virion is blocked

4. Detail: The viral neuraminidase enzyme normally cleaves the sialic acid that tethers a budding virion to the cell (and to other virions), letting it detach and go on to infect further cells; oseltamivir carboxylate (oseltamivir's active metabolite), zanamivir and peramivir all competitively inhibit this enzyme, so virions remain aggregated at the cell surface instead of spreading. [1][2][3]

5. Step: 5

5. Title: The adamantanes act at an earlier, now largely irrelevant step: viral uncoating

5. Detail: Amantadine and rimantadine block the influenza A M2 protein, an ion channel the virus needs early in entry to acidify its interior and release its genome from the matrix protein (uncoating); this mechanism only ever applied to influenza A, and it is now defeated by a resistance mutation present in essentially all circulating strains. [6][5]

Spectrum of activity

Intro: Spectrum in this class is not about a range of different microbial genera the way it is for an antibacterial - every drug here targets influenza specifically - but there is a real spectrum distinction between influenza A and influenza B coverage, and a further distinction in which viral subtypes and resistance genotypes each mechanism actually reaches.

1. Subclass: Neuraminidase inhibitors

1. Covers: Both influenza A and influenza B; oseltamivir, zanamivir and peramivir are all labelled for treatment of acute uncomplicated illness due to either type.

1. Gaps: Efficacy depends on the neuraminidase gene not carrying a resistance substitution such as H275Y (oseltamivir-specific), and none of the three treats other respiratory viruses. [1][2][3]

2. Subclass: Cap-dependent endonuclease inhibitor (baloxavir)

2. Covers: Both influenza A and influenza B, via a viral polymerase target that neuraminidase-inhibitor resistance mutations do not affect, making it a mechanistically independent option when NAI resistance is a concern.

2. Gaps: Its own resistance pathway (PA substitutions, commonly I38T) is distinct and was observed at meaningfully higher rates in paediatric than adult trial populations. [4]

3. Subclass: Adamantanes

3. Covers: Influenza A only, historically - the M2 channel they target has no equivalent in influenza B.

3. Gaps: Essentially defeated by resistance in currently circulating influenza A strains; the CDC does not recommend using this subclass for treatment or prophylaxis regardless of subtype. [5][6]

Major clinical uses

1. Drug: Oseltamivir

1. Organism: Influenza A and B virus

1. Indication: Treatment of acute uncomplicated influenza in patients 2 weeks of age and older symptomatic no more than 48 hours; prophylaxis in patients 1 year and older

1. Line: first-line oral option, including for hospitalised and pregnant patients per CDC guidance

1. Note: The only neuraminidase inhibitor with a labelled treatment indication down to 2 weeks of age. [1][5]

2. Drug: Zanamivir

2. Organism: Influenza A and B virus

2. Indication: Treatment of uncomplicated influenza in patients 7 years and older symptomatic no more than 2 days; prophylaxis in patients 5 years and older

2. Line: alternative when oral therapy is not preferred and airway disease is not present

2. Note: Avoided in patients with asthma or COPD because of bronchospasm risk. [2]

3. Drug: Peramivir

3. Organism: Influenza A and B virus

3. Indication: Treatment of acute uncomplicated influenza in patients symptomatic no more than 2 days, given as a single IV dose

3. Line: option for patients who cannot take oral or inhaled therapy reliably

3. Note: Not established as effective in patients with influenza severe enough to require hospitalisation. [3]

4. Drug: Baloxavir marboxil

4. Organism: Influenza A and B virus

4. Indication: Treatment of acute uncomplicated influenza and post-exposure prophylaxis, single oral dose

4. Line: option for outpatients within 48 hours of onset, particularly where single-dose adherence is an advantage

4. Note: Absorption reduced by dairy products, calcium-fortified beverages and polyvalent-cation antacids or laxatives, which must be avoided around dosing. [4]

5. Drug: Amantadine / rimantadine

5. Organism: Influenza A virus only (historical)

5. Indication: Not currently recommended for influenza treatment or chemoprophylaxis

5. Line: not used for this indication currently

5. Note: Retained in the curriculum as the reference example of a once-effective antiviral class made obsolete by resistance. [5][6]

Pharmacokinetics

1. Drug: Oseltamivir

1. Route: Oral

1. Absorption: Well absorbed orally; a prodrug hydrolysed to the active metabolite oseltamivir carboxylate

1. Csf Penetration: See prescribing reference

1. Metabolism: Hepatic esterase hydrolysis to the active carboxylate metabolite

1. Elimination: Renal, mainly as the active metabolite

1. Dose Adjust: Reduced dose in moderate to severe renal impairment (specific regimens set out in the label for CrCl 30-60 and lower) [1]

2. Drug: Zanamivir

2. Route: Oral inhalation

2. Absorption: Low systemic bioavailability by design; acts locally in the respiratory tract

2. Csf Penetration: See prescribing reference

2. Metabolism: Minimal metabolism

2. Elimination: Renal, largely unchanged

2. Dose Adjust: See prescribing reference for severe renal impairment [2]

3. Drug: Peramivir

3. Route: Intravenous, single dose

3. Absorption: Not applicable (IV administration)

3. Csf Penetration: See prescribing reference

3. Metabolism: Not extensively metabolised

3. Elimination: Renal, largely unchanged

3. Dose Adjust: Dose reduced in renal impairment based on creatinine clearance [3]

4. Drug: Baloxavir marboxil

4. Route: Oral, single dose

4. Absorption: Absorption reduced by co-administration with polyvalent cations (dairy, calcium-fortified beverages, certain antacids and laxatives)

4. Csf Penetration: See prescribing reference

- 4. Metabolism: Hydrolysed to the active metabolite baloxavir acid
- 4. Elimination: Primarily biliary/faecal
- 4. Dose Adjust: See prescribing reference; single-dose regimen limits the practical need for adjustment schedules [4]
- 1. This page gives no dose regimens by design. Renal-impairment dosing for oseltamivir, peramivir and zanamivir, and weight-based dosing for baloxavir, belong in a current prescribing reference used by the treating clinician.
- 2. Route is a real pharmacokinetic and practical differentiator in this class: oseltamivir's oral bioavailability supports outpatient use across a wide age range, zanamivir's inhaled route keeps systemic exposure low but requires intact inspiratory technique, and peramivir's IV route removes the absorption question entirely for a patient who cannot swallow or inhale reliably. [1][2][3]

Adverse effects

- 1. Effect: Nausea and vomiting
 - 1. Detail: The most commonly reported adverse reactions with oseltamivir in treatment studies; vomiting was the only reaction reported at a frequency of more than 1% in some paediatric populations. [1]
- 2. Effect: Headache
 - 2. Detail: Reported with oseltamivir and also among the more common reactions with baloxavir marboxil. [1][4]
- 3. Effect: Diarrhoea, bronchitis, sinusitis
 - 3. Detail: The most common adverse reactions reported with baloxavir marboxil in clinical trials, each in the low single-digit percentages. [4]
- 1. Effect: Neuropsychiatric events (delirium, abnormal behaviour)
 - 1. Detail: Postmarketing reports describe delirium and abnormal behaviour leading to injury in patients, predominantly paediatric, taking oseltamivir; the label specifically recommends closely monitoring patients with influenza for signs of abnormal behaviour during treatment.
 - 1. Action: Patients and caregivers are advised to seek medical attention promptly if unusual behaviour develops during treatment. [1]
- 2. Effect: Serious hypersensitivity, including anaphylaxis and angioedema
 - 2. Detail: Reported with baloxavir marboxil.
 - 2. Action: Discontinue if a hypersensitivity reaction occurs. [4]
- 3. Effect: Bronchospasm
 - 3. Detail: Zanamivir carries a specific risk of serious bronchospasm, including in patients without a prior history of airway disease, and is not recommended for patients with underlying asthma or COPD.
 - 3. Action: Zanamivir is avoided in patients with reactive airway disease, and a fast-acting bronchodilator should be available if it is used in a patient with any airway disease. [2]
- 1. Drug: Oseltamivir
 - 1. Effect: The specific neuropsychiatric monitoring recommendation and the H275Y resistance concern are unique among this drug's own labelling emphasis, reflecting both its broad paediatric use and its dominant real-world usage volume. [1]
- 2. Drug: Zanamivir
 - 2. Effect: Inhalation route carries the class's specific bronchospasm warning, not shared by the oral or IV agents. [2]
- 3. Drug: Peramivir
 - 3. Effect: Its efficacy has specifically not been established in patients with influenza serious enough to require hospitalisation, a limitation stated directly in its own label rather than a general class caveat. [3]
- 4. Drug: Baloxavir marboxil
 - 4. Effect: Uniquely subject to a food/polyvalent-cation interaction that meaningfully lowers drug absorption if not avoided around dosing. [4]

Contraindications, precautions and interactions

1. Oseltamivir: known serious hypersensitivity to oseltamivir or any component of the product. [1]
2. Baloxavir marboxil: history of hypersensitivity to baloxavir marboxil or any of its ingredients. [4]
1. Zanamivir is not recommended for patients with underlying airway disease such as asthma or COPD because of the risk of serious bronchospasm. [2]
2. Patients on any of these drugs, especially paediatric patients on oseltamivir, are monitored for signs of abnormal behaviour during the acute illness. [1]
3. Peramivir's efficacy is not established in patients sick enough to need hospitalisation, which is a caution about expected benefit rather than a safety contraindication. [3]
1. With: Dairy products, calcium-fortified beverages, polyvalent-cation-containing laxatives and antacids
1. Effect: Chelate baloxavir marboxil and reduce its absorption; co-administration around the dose is avoided. [4]
2. With: Live attenuated influenza vaccine
2. Effect: Antiviral activity against the vaccine virus is a general consideration with any influenza antiviral used near the time of live vaccine administration and is addressed in current immunisation guidance rather than restated here in detail. [5]

Resistance mechanisms

Intro: Each of the two currently recommended mechanisms has its own, mechanistically distinct resistance pathway, and the adamantane class is the clearest teaching example in this whole page of a resistance mutation becoming essentially universal in circulating virus.

1. Mechanism: Neuraminidase active-site substitution (H275Y and related mutations)
1. Organism: Influenza A, particularly historical seasonal H1N1 lineages
1. Impact: The H275Y substitution in the neuraminidase gene reduces oseltamivir (and cross-reactively, peramivir) binding; it was found in more than 99% of US-circulating 2008 seasonal H1N1 isolates before that lineage was displaced by the 2009 pandemic strain. [1]
2. Mechanism: Polymerase acidic (PA) protein substitutions, notably I38T
2. Organism: Influenza A and B
2. Impact: Treatment-emergent PA substitutions reduce baloxavir susceptibility and were detected in clinical trials at roughly 4.5-10.9% of treated adults and adolescents but substantially more often, about 20-27.9%, in treated children. [4]
3. Mechanism: M2 ion channel substitution (adamantane resistance)
3. Organism: Influenza A
3. Impact: A single amino-acid change in the M2 channel confers adamantane resistance; this became dominant in circulating influenza A (H3N2) from the 2005-2006 season onward and is also present in influenza A(H1N1)pdm09, which is why the CDC no longer recommends amantadine or rimantadine for treatment or prophylaxis of currently circulating strains. [5][6]

Comparison tables

Title: Two mechanisms, two resistance pathways, one shared time window

Caption: All four currently recommended drugs share the same 48-hour treatment-window logic, but each blocks a different step of the influenza life cycle and each has developed its own distinct resistance pathway.

1. Key: drug
1. Label: Drug
2. Key: route
2. Label: Route

- 3. Key: target
- 3. Label: Molecular target
- 4. Key: resistance
- 4. Label: Known resistance pathway
- 1. Drug: Oseltamivir
- 1. Route: Oral
- 1. Target: Viral neuraminidase
- 1. Resistance: H275Y neuraminidase substitution [1]
- 2. Drug: Zanamivir
- 2. Route: Inhaled
- 2. Target: Viral neuraminidase
- 2. Resistance: Neuraminidase substitutions; cross-resistance with oseltamivir variable by mutation [2]
- 3. Drug: Peramivir
- 3. Route: Intravenous
- 3. Target: Viral neuraminidase
- 3. Resistance: Neuraminidase substitutions including H275Y [3]
- 4. Drug: Baloxavir marboxil
- 4. Route: Oral, single dose
- 4. Target: Polymerase acidic (PA) endonuclease
- 4. Resistance: PA substitutions, commonly I38T [4]
- 5. Drug: Amantadine / rimantadine
- 5. Route: Oral
- 5. Target: M2 ion channel (influenza A only)
- 5. Resistance: M2 substitution now dominant in circulating influenza A; not currently recommended for use [5][6]

High-yield exam pearls

- 1. Pearl: Neuraminidase inhibitors act at viral release; baloxavir acts at viral transcription - two genuinely different steps of the replication cycle, not two versions of the same idea.
- 1. Why: This is the single most testable structural fact about the class and explains why baloxavir resistance is mechanistically independent of neuraminidase-inhibitor resistance. [1][4]
- 2. Pearl: The 48-hour rule is not a soft suggestion - it is written into the indication itself for acute uncomplicated influenza treatment across this class.
- 2. Why: Both oseltamivir's and baloxavir's own labels define the treated population as symptomatic no more than 48 hours; starting later moves outside the population the drug was shown to help. [1][4]
- 3. Pearl: H275Y is the exam's go-to oseltamivir-resistance mutation, and it became essentially universal in one specific historical seasonal H1N1 lineage before that lineage was replaced.
- 3. Why: The magnitude (>99% of 2008 US isolates) is a striking, testable number, and the fact that the resistant lineage was later displaced (not eradicated by better drug use) is a subtlety that catches out an oversimplified telling. [1]
- 4. Pearl: Zanamivir's bronchospasm warning is inhalation-route-specific, not a class-wide adverse effect.
- 4. Why: Confusing it with a general neuraminidase-inhibitor risk would wrongly restrict oseltamivir or peramivir use in a patient with asthma. [2]
- 5. Pearl: Amantadine and rimantadine only ever worked against influenza A, never influenza B, because the drugs target the M2 channel that influenza B does not have in the same form.
- 5. Why: It is a clean example of a mechanism-based spectrum gap that predates and is separate from the resistance story that later ended the adamantanes' clinical use entirely. [6]

Common exam traps

1. Trap: Assuming baloxavir is just a longer-acting neuraminidase inhibitor.
 1. Correction: It targets an entirely different viral enzyme (the PA endonuclease of the polymerase complex) acting earlier in the replication cycle, which is why baloxavir resistance and neuraminidase-inhibitor resistance are separate, non-overlapping phenomena. [4]
2. Trap: Treating amantadine and rimantadine as current first-line influenza options because they still appear in older pharmacology material.
 2. Correction: The CDC explicitly does not recommend either drug for influenza treatment or chemoprophylaxis because of high resistance in circulating influenza A strains, and neither has ever covered influenza B. [5][6]
3. Trap: Assuming zanamivir's bronchospasm risk applies to oral or IV neuraminidase inhibitors too.
 3. Correction: The warning is specific to the inhaled route and the direct airway exposure it produces; it is not stated as a class-wide risk in the oseltamivir or peramivir labels. [2]
4. Trap: Believing the 48-hour window means these drugs are useless after 48 hours in every patient.
 4. Correction: The labelled indication for uncomplicated outpatient illness is built around that window, but CDC guidance notes hospitalised patients with severe or progressive disease may still be treated afterward, since the trial population and the sickest inpatient population are not identical. [5]

Self-test questions

1. Question: What viral enzyme do oseltamivir, zanamivir and peramivir all inhibit?
 1. The PA endonuclease of the viral polymerase
 2. Viral neuraminidase
 3. The M2 ion channel
 4. Viral haemagglutinin
 1. Explanation: All three are neuraminidase inhibitors: they block the enzyme that cleaves sialic acid to release newly assembled virions from the infected cell surface. [1][2][3]
2. Question: How does baloxavir marboxil's mechanism differ from that of the neuraminidase inhibitors?
 1. It also inhibits neuraminidase but with longer duration
 2. It inhibits the endonuclease activity of the viral polymerase acidic protein, blocking cap-snatching and mRNA transcription
 3. It blocks the M2 ion channel
 4. It has no antiviral mechanism and works only symptomatically
 2. Explanation: Baloxavir inhibits the PA endonuclease, an earlier step in the replication cycle (viral transcription) than the neuraminidase inhibitors' target (viral release). [4]
3. Question: Which resistance mutation is specifically associated with oseltamivir and became dominant in one historical seasonal influenza lineage?
 1. I38T
 2. M2 S31N
 3. H275Y
 4. PA/E23K
 3. Explanation: H275Y in the neuraminidase gene reduces oseltamivir binding and was found in more than 99% of US-circulating 2008 seasonal H1N1 isolates. [1]
4. Question: Why is zanamivir avoided in patients with asthma or COPD?
 1. It causes hepatotoxicity in these patients
 2. It carries a specific risk of serious bronchospasm because it is delivered by oral inhalation
 3. It is ineffective against influenza in these patients
 4. It requires an IV line that these patients cannot tolerate

4. Explanation: Zanamivir's own label carries a specific warning about serious bronchospasm, including in patients without prior airway disease, and it is not recommended for patients with asthma or COPD. [2]
5. Question: What is the current status of amantadine and rimantadine for influenza?
 1. First-line therapy for influenza A and B
 2. Not recommended for treatment or chemoprophylaxis because of high resistance among circulating influenza A viruses, and never active against influenza B
 3. Reserved for hospitalised patients only
 4. Recommended only in children under 2 weeks of age
5. Explanation: The CDC states these adamantanes are not recommended because of high-level resistance in circulating influenza A, and they were never active against influenza B, which has a structurally different M2-equivalent protein. [5][6]
6. Question: Within what time frame from symptom onset is treatment with oseltamivir or baloxavir indicated for uncomplicated outpatient influenza?
 1. 7 days
 2. 48 hours
 3. 24 hours only
 4. There is no time limit specified in the label
6. Explanation: Both labels define the treated population for acute uncomplicated influenza as patients symptomatic for no more than 48 hours, reflecting where the clinical trial benefit was demonstrated. [1][4]

Frequently asked questions

1. Question: Do influenza antivirals cure the flu?
 1. Answer: No. They are meant to shorten the duration of illness and reduce the risk of complications when started early, not to eliminate an already-established infection instantly. The clinical trial evidence behind all four current agents was generated in patients treated within 48 hours of symptom onset, which is why that window is written into the indication itself. [1][4][5]
 2. Question: Is baloxavir a replacement for oseltamivir?
 2. Answer: It is an alternative with a different mechanism and a single-dose regimen, not a universal replacement. Because it targets the viral polymerase rather than neuraminidase, it remains active against neuraminidase-inhibitor-resistant strains, but it has developed its own resistance pathway (PA substitutions such as I38T), which was seen more often in children than adults in trials. [4]
 3. Question: Why are amantadine and rimantadine still taught if they are not used?
 3. Answer: They remain a clear teaching example of a viral resistance mutation becoming essentially universal in circulating strains and permanently changing prescribing guidance. The CDC's current position is that neither drug should be used for influenza treatment or prophylaxis because of high resistance among circulating influenza A viruses, and neither ever worked against influenza B. [5][6]
 4. Question: Can zanamivir be used in someone with asthma?
 4. Answer: It is not recommended for patients with underlying airway disease such as asthma or COPD, because of a labelled risk of serious bronchospasm with the inhaled route, including in patients without a prior history of airway disease. An oral or intravenous neuraminidase inhibitor, or baloxavir, would be considered instead for such a patient by the treating clinician. [2]

References

- [1] TAMIFLU (oseltamivir phosphate) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1b28c7c8-08c7-5ee9-e063-6394a90a7210>
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