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Antiviral Drugs for Influenza

Influenza is generally a self-limited illness, but pneumonia, respiratory failure, and death can occur. Health Canada- and FDA-approved antiviral drugs for influenza are listed in Table 2. The neuraminidase inhibitors oseltamivir (Tamiflu, and generics), which is taken orally, and zanamivir (Relenza), which is inhaled, are approved for prophylaxis and treatment of acute uncomplicated influenza. The IV neuraminidase inhibitor peramivir (Rapивab; approved but not available in Canada) and the oral polymerase acidic (PA) endonuclease inhibitor baloxavir marboxil (Xofluza; not approved in Canada) are approved only for treatment. 1,2 All of these drugs are active against both influenza A and influenza B viruses. Updated information on influenza activity and antiviral resistance is available from Health Canada at [http://bit.ly/2sjzogq](http://bit.ly/2sjzogq) and from the CDC at [www.cdc.gov/flu](http://www.cdc.gov/flu).

**INDICATIONS FOR TREATMENT** — Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza infection who is hospitalized, has severe, complicated, or progressive illness, or is at high risk for influenza complications (see Table 1).3-5 False negative results can occur with some influenza tests; patients with suspected influenza infection who have severe, complicated, or progressive illness or are at high risk for influenza complications should receive antiviral treatment despite a negative test result, especially when influenza is known to be circulating in the community.5

Antiviral treatment can be considered for previously healthy persons with suspected or confirmed influenza who are not at high risk for influenza complications if it can be started within 48 hours of illness onset.

**CHOICE OF DRUGS** — For treatment of nonpregnant outpatients with acute uncomplicated influenza, the CDC recommends oseltamivir, zanamivir, peramivir, or baloxavir. There are no data suggesting that one drug is more effective than any other in such patients. Oseltamivir is preferred for treatment of pregnant women, hospitalized patients, and outpatients with severe, complicated, or progressive influenza illness.3

**PROPHYLAXIS** — Antiviral prophylaxis is recommended to help control institutional influenza outbreaks. It can be considered after exposure for persons at high risk for complications who have not received influenza vaccine this season, received it within the previous 2 weeks, or are unlikely to have responded to vaccination, such as those who are immunosuppressed. Prophylaxis is not recommended for healthy persons exposed to influenza or when >48 hours have elapsed since exposure.3

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**Table 1: Patients at High Risk for Influenza Complications**

- Children <5 years old (children <2 years old are at highest risk)
- Patients <19 years old receiving long-term treatment with aspirin or salicylate-containing drugs
- Adults ≥65 years old
- Extremely obese patients (BMI ≥40)
- Women who are pregnant or ≤2 weeks postpartum
- Persons of American Indian or Alaska Native heritage
- Residents of nursing homes or other chronic care facilities
- Patients who are immunosuppressed or have chronic medical conditions

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**Summary: Treatment of Influenza**

- Antiviral treatment is recommended for patients with suspected or confirmed influenza who are at high risk for influenza complications, for hospitalized patients, and for outpatients with severe, complicated, or progressive illness.
- Antiviral treatment should be started as soon as possible; it is most effective when started within 48 hours of illness onset.
- Antiviral treatment can be considered for previously healthy persons with suspected or confirmed influenza who are not at high risk for influenza complications if it can be started within 48 hours of illness onset.
- The CDC recommends oral oseltamivir, inhaled zanamivir, IV peramivir, or oral baloxavir for treatment of nonpregnant outpatients with acute uncomplicated influenza.
- Oseltamivir is the drug of choice for treatment of pregnant women, hospitalized patients, and outpatients with severe, complicated, or progressive influenza illness.
Table 2. Antiviral Drugs for Influenza\(^1\)

| Drug                          | Formulations                                      | Usual Treatment Dosage                                      | Usual Prophylaxis Dosage                                      | US Cost\(^2\) | CAN Cost\(^3\)
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir (^3) – generic</td>
<td>30, 45, 75 mg caps; Tamiflu (Hoffmann) 6 mg/mL oral susp(^7)</td>
<td>≥2 wks-&lt;1 yr: 3 mg/kg PO bid(^{16})</td>
<td>&lt;1 yr: 3 mg/kg PO once/day(^{4,16})</td>
<td>$80.00</td>
<td>$31.20</td>
</tr>
<tr>
<td></td>
<td>La Roche; Genentech in US)</td>
<td>x 5 days(^{12,17})</td>
<td>x 7 days(^{13,17})</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-12 yrs: 30-75 mg PO bid(^{11})</td>
<td>1-12 yrs: 30-75 mg PO once/day(^{11})</td>
<td>151.90</td>
<td>44.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x 5 days(^{10})</td>
<td>x 7 days(^{10})</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥13 yrs: 75 mg PO bid(^{10}) x 5 days(^{11})</td>
<td>≥13 yrs: 75 mg PO once/day(^{4,11}) x 7 days(^{10})</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal Impairment: See footnote 12</td>
<td>Renal Impairment: See footnote 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peramivir (^12) – Rapivab (BioCryst)</td>
<td>200 mg/20 mL single-use vials</td>
<td>2-12 yrs: 12 mg/kg (max 600 mg) IV once(^{14})</td>
<td>Not FDA-approved for prophylaxis</td>
<td>950.00</td>
<td>N.A.C.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥13 yrs: 600 mg IV once(^{14})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal Impairment: See footnote 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanamivir (^{2,16}) – Relenza (GSK)</td>
<td>5 mg blisters of powder for inhalation(^{17})</td>
<td>≥7 yrs: 2 inhalations bid x 5 days(^{17})</td>
<td>≥5 yrs: 2 inhalations once/day x 7 days(^{5,17,12})</td>
<td>$9.00</td>
<td>$39.20</td>
</tr>
<tr>
<td>Polymeric Acidic (PA) Endonuclease Inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baloxavir marboxil (^{18}) – Xofluza (Shionogi/Genentech)</td>
<td>20, 40 mg tabs in 2-tablet blister packs</td>
<td>≥12 years and ≈80 kg: 40 mg PO once(^{18})</td>
<td>Not FDA-approved for prophylaxis</td>
<td>150.00</td>
<td>N.A.C.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥13 years and ≈80 kg: 80 mg PO once(^{19})</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.A.C. = Not available in Canada

1. Use of amantadine and rimantadine is not recommended because of high levels of resistance to these drugs among currently circulating influenza A viruses; they are not active against influenza B viruses.
2. Approximate WAC for 5 days’ treatment with oseltamivir capsules or zanamivir, or for a single treatment dose of peramivir or baloxavir; at the usual adult dosage. WAC = wholesaler acquisition cost, or manufacturer’s published catalogue or list prices and may not represent an actual transactional price. Source: AnalySource® Monthly. December 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
4. Capsules can be opened and the contents mixed in a thick sweetened liquid (e.g., chocolate syrup, corn syrup, caramel topping, or brown sugar dissolved in water) to mask the bitter taste and consumed immediately.
5. Although not FDA-approved for use in children <2 weeks old, the CDC recommends children <2 weeks old be treated with 3 mg/kg bid. The American Academy of Pediatrics has recommended a dose of 3.5 mg/kg for infants 9-11 months old based on the results of a study showing that a higher dose was needed to achieve the target exposure in this age group (DW Kimberlin et al. J Infect Dis 2013; 207:709). For treatment of premature infants, refer to CDC recommendations (www.cdc.gov/flu).
6. Taking oseltamivir with food may improve tolerability.
7. In hospitalized, critically ill, or immunocompromised patients, a longer treatment course of oseltamivir (e.g., 10 days) is often used. Oseltamivir can be administered by oro/nasogastric tube to patients who are unable to swallow. IV peramivir (for at least 5 days) may be considered for those who cannot tolerate or absorb oral or enterically administered oseltamivir because of gastric stasis, malabsorption, or GI bleeding.
8. Although not FDA-approved for prophylaxis in children <1 year old, the American Academy of Pediatrics and CDC recommend that children 3 months–<1 year old receive 3 mg/kg once/day. Prophylaxis is generally not recommended for premature infants or infants <3 months old (refer to CDC recommendations at: www.cdc.gov/flu).
9. Duration of prophylaxis recommended by the CDC is 7 days after the last known exposure. The recommended duration in the labeling of oseltamivir and zanamivir is 10 days.
10. For control of outbreaks in institutions, the CDC recommends prophylaxis be given for at least 2 weeks and continued for up to 1 week after the end of the outbreak. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised patients.
11. FDA-approved doses for children 1-12 years old: <15 kg: 30 mg; >15-23 kg: 45 mg; >23-40 kg: 60 mg; >40 kg: 75 mg.
12. Oseltamivir renal dosage adjustment for adults and children who weigh >40 kg (recommended by the CDC): CrCl 30-60 mL/min: 30 mg bid for treatment and 30 mg once/day for prophylaxis; CrCl 10-30 mL/min: 20 mg once/day for both treatment and prophylaxis; CrCl <10 mL/min: 10 mg once/day for both treatment and prophylaxis; kidney transplantation: 30 mg once every 12 hours for treatment and 15 mg once every 12 hours for prophylaxis. End-stage renal disease (ESRD) not on HD: 30 mg once every 12 hours for both treatment and prophylaxis. Children: 3 mg/kg once/day.
13. FDA-approved for treatment of acute uncomplicated influenza in otherwise healthy patients. Not FDA-approved, but used off-label, for treatment of severe or complicated influenza illness.
15. Peramivir renal dosage adjustment for patients 2-12 years old: CrCl 30-49 mL/min: 4 mg/kg once; CrCl 10-29 mL/min: 2 mg/kg once. For patients ≥13 years old: CrCl 30-49 mL/min: 200 mg once; CrCl 10-29 mL/min: 100 mg once, hemodialysis (HD): administer dose (based on CrCl) after HD.
16. Inhaled zanamivir is not recommended for use in patients with underlying respiratory disease such as asthma or COPD, or in patients with severe influenza, including hospitalized patients. It is contraindicated in patients with a history of milk protein allergy.
17. Available in a carton containing 5 rotadisks (each rotadisk contains four 5-mg blisters of the active drug in a lactose carrier) and a Diskhaler inhalation device. Zanamivir should not be used in a nebulizer.
18. FDA-approved for treatment of acute uncomplicated influenza in otherwise healthy patients and in those at high risk of developing influenza-related complications. Not FDA-approved for prophylaxis or treatment of severe or complicated influenza illness. CDC does not recommend baloxavir monotherapy in severely immunosuppressed patients because of concerns that resistance could emerge due to prolonged influenza virus replication in these patients.
19. Coadministration of dairy products, calcium-fortified beverages, or products containing polyvalent cations such as calcium, aluminum, iron, magnesium, selenium, or zinc should be avoided.
20. Average WAC for 5 days’ treatment with oseltamivir capsules or zanamivir at the usual adult dosage, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, December 2019).
21. Suspension not available generically.
22. Not approved in Canada for children <1 year of age.
23. In Canada, ≥7 years, 2 inhalations once/day x 10 days.

**EFFECTIVENESS — Treatment** — Use of a neuraminidase inhibitor or baloxavir for treatment of acute uncomplicated influenza in adults shortens the duration of symptoms by about a day.\(^7\)\(^-\)\(^9\) A meta-analysis of randomized trials in children with influenza found that starting treatment with oseltamivir within 48 hours of symptom onset reduced illness duration by about 18 hours (by 30 hours when trials that enrolled only children with asthma were excluded) and reduced the risk of developing otitis media.\(^10\) Although most controlled trials of these drugs have not been powered to assess their efficacy in preventing serious influenza complications, experts have generally interpreted the combined results of controlled trials, observational
studies, and meta-analyses as showing that early antiviral treatment of influenza in high-risk patients can reduce the risk of complications.7,11-13

In clinical trials in healthy outpatients ≥12 years old with uncomplicated influenza, administration of baloxavir within 48 hours of symptom onset shortened the duration of influenza symptoms by about a day compared to placebo; the time to alleviation of symptoms was about the same with baloxavir and oseltamivir.9 Similar results were reported in a trial in patients at high risk for influenza complications.14

No controlled trials are available on use of baloxavir for treatment of influenza in immunocompromised or hospitalized patients, or in those with severe influenza.

**Prophylaxis** — Neuraminidase inhibitors have generally been about 70-90% effective when used for prophylaxis against susceptible strains of influenza A or B viruses.3

In one trial (BLOCKSTONE; available only as a press release), a single dose of baloxavir was effective when used for prophylaxis, but it is not approved by the FDA for such use.

**TIMING — Treatment** — Neuraminidase inhibitors are most effective when started within 48 hours of illness onset, but complications of influenza can occur ≥48 hours after illness onset. The results of some observational studies in hospitalized and critically ill patients suggest that treatment started as late as 4-5 days after illness onset can reduce the risk of complications such as pneumonia, respiratory failure, and death.15-17 Adults (outpatient or hospitalized) with community-acquired pneumonia (CAP) who test positive for influenza should receive antiviral treatment regardless of the duration of illness.18 No data are available on the efficacy of baloxavir started ≥48 hours after symptom onset.

**Prophylaxis** — When indicated, prophylaxis with oseltamivir or zanamivir should be started within 48 hours after exposure to the influenza virus and continued for 7 days after the last known exposure. For institutional outbreaks, the CDC recommends prophylaxis be given for at least 2 weeks and continued for up to 1 week after the end of the outbreak.

**PREGNANCY AND LACTATION** — Pregnant women are at increased risk for severe complications of influenza, including death. Oseltamivir and zanamivir appear to be safe for use during pregnancy.19,20 Prompt treatment with oseltamivir is recommended for women with suspected or confirmed influenza who are pregnant or ≤2 weeks postpartum.21-23 Oseltamivir, which is minimally excreted in breast milk, is also preferred for treatment of women who are breastfeeding. No data are available on use of baloxavir during pregnancy or while breastfeeding.

Antiviral prophylaxis can be considered for pregnant women who have had close contact with someone likely to have been infected with influenza. Zanamivir may be preferred for prophylaxis because of its limited systemic absorption, but oseltamivir is a reasonable alternative, especially in women at increased risk for respiratory problems.

**RESISTANCE** — Nearly all (>99%) of the recently circulating influenza virus strains tested by the World Health Organization (WHO) have been susceptible to neuraminidase inhibitors.24 Reduced susceptibility of some influenza strains, particularly influenza A(H1N1), to oseltamivir or peramivir can emerge during or after treatment, especially in immunocompromised patients with prolonged viral shedding and in young children.25-28 Resistant isolates have usually remained susceptible to zanamivir, but reduced susceptibility to zanamivir has been reported.29,30 In immunocompromised patients, use of a double dose of oseltamivir reduced the incidence of oseltamivir resistance compared to standard dosing, but it can cause more adverse effects.31

Baloxavir is active against neuraminidase inhibitor-resistant strains of influenza A and B viruses, including A(H1N1), A(H5N1), and A(H3N2). Amino acid substitutions associated with reduced susceptibility to baloxavir have occurred following treatment with a single dose.9 Reduced susceptibility to baloxavir appears to be more frequent in influenza A(H3N2) viruses and in children, and person-to-person transmission of resistant strains may occur.25,32 Baloxavir is not recommended for severely immunosuppressed patients because of concerns that prolonged replication of the influenza virus in these patients could lead to emergence of resistance. Oseltamivir and peramivir may be active against influenza strains with reduced susceptibility to baloxavir.34

**ADVERSE EFFECTS** — Nausea, vomiting, and headache are the most common adverse effects of oseltamivir; taking the drug with food may minimize GI adverse effects. Diarrhea, nausea, sinusitis, fever, and arthralgia have been reported with zanamivir. Inhalation of zanamivir can cause bronchospasm; the drug should not be used in patients with underlying airway disease. Diarrhea and neutropenia have occurred with peramivir.

Neuropsychiatric events, including self-injury and delirium, have been reported in patients taking neuraminidase inhibitors, but a causal relationship has not been established, and neuropsychiatric dysfunction can be a complication of influenza illness.35
Baloxavir was well tolerated in clinical trials. It appears to cause less nausea and vomiting than oseltamivir.2

**DRUG INTERACTIONS** — Use of a neuraminidase inhibitor or baloxavir within 48 hours before or <2 weeks after administration of the intranasal live-attenuated influenza vaccine *(FluMist Quadrivalent;* not available in Canada) could inhibit replication of the vaccine virus, reducing the vaccine's efficacy.

Coadministration of antacids, laxatives, multivitamins, or other products containing polyvalent cations such as calcium, aluminum, iron, magnesium, selenium, or zinc can reduce serum concentrations of baloxavir and should be avoided.

32. E Takashita et al. Influenza A(H3N2) virus exhibiting reduced susceptibility to baloxavir due to a polymerase acidic subunit 138T substitution detected from a hospitalized child before baloxavir treatment, Japan, January 2019. Euro Surveill 2019; 24 pii:1900170.
34. M Seki et al. Adult influenza A (H3N2) with reduced susceptibility to baloxavir or peramivir cured after switching anti-influenza agents. ID Cases 2019; 18:e00650.
Ivacaftor is available alone for mutation. This is the least one copy of the Phe508del (also called F508del) mutation. About 90% of patients with CF have at least one Phe508del mutation in the CFTR gene. About 90% of patients with CF have at least one Phe508del mutation in the CFTR gene. About 90% of patients with CF have at least one Phe508del mutation in the CFTR gene. About 90% of patients with CF have at least one Phe508del mutation in the CFTR gene. About 90% of patients with CF have at least one Phe508del mutation in the CFTR gene.

MECHANISM OF ACTION — The CFTR protein functions as a regulated chloride channel. Mutations in the CFTR gene, which encodes the CFTR protein, are the cause of CF. CFTR modulators correct defects in the CFTR protein caused by genetic mutations. The Phe508del mutation, the most common CFTR mutation, causes abnormal CFTR folding and trafficking, resulting in a reduced quantity of CFTR protein at the cell surface and disruption of channel gating. Ivacaftor and tezacaftor improve cellular processing and trafficking of Phe508del-CFTR, which increases the amount of CFTR at the cell surface. Ivacaftor increases chloride channel transport by augmenting channel gating.

Table 1. Pharmacology

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Tmax (median)</th>
<th>Metabolism</th>
<th>Elimination</th>
<th>Half-life (mean effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eluxacaftor</td>
<td>6 hours</td>
<td>Primarily hepatic by CYP3A4/5</td>
<td>Feces (87.3%); urine (0.23%)</td>
<td>29.8 hours</td>
</tr>
<tr>
<td>Tezacaftor</td>
<td>3 hours</td>
<td>Primarily hepatic by CYP3A4/5</td>
<td>Feces (72%); urine (14%)</td>
<td>17.4 hours</td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>4 hours</td>
<td>Primarily hepatic by CYP3A4/5</td>
<td>Feces (87.8%); urine (6.6%)</td>
<td>15.0 hours</td>
</tr>
</tbody>
</table>

OTHER COMBINATIONS — Lumacaftor/ivacaftor and tezacaftor/ivacaftor have been shown to improve pulmonary function and reduce pulmonary exacerbations in the approximately 50% of CF patients who are homozygous for the Phe508del mutation. Tezacaftor/ivacaftor can also be used in CF patients who have at least one CFTR mutation that is responsive to the combination. Tezacaftor/ivacaftor has fewer drug interactions than lumacaftor/ivacaftor, and it appears to have fewer adverse effects. However, neither of these combinations restores Phe508del-CFTR function adequately in patients with a single Phe508del mutation and one minimal-function mutation (a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor).

CLINICAL STUDIES — FDA approval of the triple combination was based on the results of 2 randomized, double-blind trials in CF patients ≥12 years old. Trial 1 was a 24-week trial comparing eluxacaftor/tezacaftor/ivacaftor to placebo in 403 patients with one Phe508del mutation and one minimal-function mutation. Trial 2 was a 4-week trial comparing the triple combination to tezacaftor/ivacaftor in 107 patients who were homozygous for the Phe508del mutation. In both trials, use of the triple combination compared to placebo or tezacaftor/ivacaftor resulted in a significant improvement from baseline in mean percent predicted forced expiratory volume in 1 second (ppFEV₁) at 4 weeks (the primary endpoint). In Trial 1, the improvement in ppFEV₁ was sustained through week 24 and the number of pulmonary exacerbations was significantly improved from baseline.

Table 2. Trikafta Clinical Trial Results

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Change in ppFEV₁ (%) pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1 (n=403; 24 weeks)</td>
<td>+13.8 at 4 weeks*</td>
</tr>
<tr>
<td>Eluxacaftor/tezacaftor/ivacaftor compared to placebo</td>
<td>+14.3 through 24 weeks*</td>
</tr>
<tr>
<td>Trial 2 (n=107; 4 weeks)</td>
<td>+10.0 at 4 weeks*</td>
</tr>
<tr>
<td>Eluxacaftor/tezacaftor/ivacaftor compared to tezacaftor/ivacaftor</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant vs comparator (p<0.001) ppFEV₁ = percent predicted forced expiratory volume in 1 second

1. Least squares mean difference between Trikafta and the comparator for the absolute change in ppFEV₁ from baseline at week 4 (primary endpoint in Trials 1 and 2) or through week 24 (secondary endpoint in Trial 1). Mean ppFEV₁ at baseline was 61.6% in Trial 1 and 60.9% in Trial 2.
2. In patients with a Phe508del mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor.
3. In patients who were homozygous for the Phe508del mutation.
Table 3. CFTR Modulators for Cystic Fibrosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-Approved Indications</th>
<th>Formulations</th>
<th>Usual Dosage1</th>
<th>US Cost2</th>
<th>CAN Cost8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor – Kalydeco (Vertex)</td>
<td>≥6 months old with a responsive mutation19</td>
<td>150 mg tabs; 50, 75 mg granule packets4</td>
<td>6 months-&lt;6 years: weight-based10</td>
<td>≥6 years: 150 mg q12 hrs11</td>
<td>$23,896</td>
</tr>
<tr>
<td>Lumacaftor/ivacaftor – Orkambi (Vertex)</td>
<td>≥2 years old, Phe508del-homozygous</td>
<td>100/125, 200/125 mg tabs; 100/125, 150/188 mg granule packets4</td>
<td>2-5 years: weight-based6</td>
<td>6-11 years: 200/250 mg q12 hrs</td>
<td>20,919</td>
</tr>
<tr>
<td>Tezacaftor/ivacaftor – Symdeko (Vertex)</td>
<td>≥6 months old, Phe508del-homozygous or Phe508del-heterozygous with another responsive mutation12</td>
<td>50/75, 100/150 mg tabs copackaged with ivacaftor 75 or 150 mg tabs</td>
<td>≥6-11 years (&lt;30 kg): 50/75 mg qAM, then 75 mg ivacaftor qPM</td>
<td>≥6 years (&lt;30 kg): 100/150 mg qAM, then 150 mg ivacaftor qPM13</td>
<td>22,400</td>
</tr>
<tr>
<td>Elexacaftor/tezacaftor/ivacaftor – Trikafta (Vertex)</td>
<td>≥12 years old, Phe508del-homozygous or Phe508del-heterozygous</td>
<td>100/50/75 mg tabs copackaged with ivacaftor 150 mg tabs</td>
<td>≥12 years: 200/100/150 mg qAM, then 150 mg ivacaftor qPM</td>
<td>23,896</td>
<td>N.A.C.</td>
</tr>
</tbody>
</table>

N.A.C. = Not available in Canada
1. Each dose should be taken with fat-containing food. Dosage reductions are required for moderate to severe hepatic impairment.
2. Approximate WAC for 4 weeks of treatment at the usual adult dosage. WAC = wholesaler acquisition cost, or manufacturer’s published price to wholesalers; WAC represents published catalogue or list prices and may not represent an actual transactional price. Source: AnalySource® Monthly. December 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
3. Responsive mutations are those in which chloride transport is expected to increase to at least 10% of untreated normal over baseline with drug therapy, based on clinical or in vitro data.
4. The granules should be mixed with 5 mL of room-temperature or cold soft food or liquid and consumed within 1 hour.
5. In patients 6 months to <6 years old, the recommended dosage is 25 mg q12 hours for those weighing 5 to <7 kg, 50 mg q12 hours for those weighing 7 to <14 kg, and 75 mg q12 hours for those weighing ≥14 kg.
6. In patients 2-5 years old, the recommended dosage is 100/125 mg q12 hours for those weighing <14 kg, and 150/188 mg q12 hours for those weighing ≥14 kg.
7. Trikafta should not be used in patients with severe hepatic impairment.
8. Approximate WAC for 4 weeks of treatment at the usual adult dosage, based on prices in Canadian dollars from the manufacturer.
9. ≥12 months old with a responsive mutation in Canada.
10. In Canada, ≥12 months old: weight based. 7 kg-14 kg: 150 mg q12 hours; ≥14 to <25 kg: 75 mg q12 hours.
11. In Canada, ≥25 kg: 150 mg q12 hours.

lower through week 24 with the combination (41 vs 113 with placebo). Use of the combination also led to a significant improvement in respiratory-related quality of life, a significant decrease in sweat chloride concentrations, and an increase in weight.

ADVERSE EFFECTS – Adverse effects of elexacaftor/tezacaftor/ivacaftor that occurred more often than with placebo in the 24-week trial included upper respiratory tract infection (16% vs 12%), influenza (7% vs 1%), abdominal pain (14% vs 9%), diarrhea (13% vs 7%), and rash (10% vs 5%). Discontinuation due to adverse effects occurred in 1% of patients taking the combination and in 0% of those taking placebo. Rash was more common in female patients than in male patients, particularly in those who were also taking hormonal contraceptives. Lens opacities have occurred in pediatric patients treated with ivacaftor-containing regimens.

In the 24-week trial, use of the triple combination compared to placebo was associated with an increase in hepatic transaminases (11% vs 4%), serum bilirubin levels >2x ULN (4% vs <1%), and creatine phosphokinase levels >5x ULN (10% vs 5%). Small increases in blood pressure were reported with the combination.

DRUG INTERACTIONS – Elexacaftor, tezacaftor, and ivacaftor are substrates of CYP3A. The triple combination should not be taken with a strong CYP3A inducer, and dosage reductions are required when it is taken with a strong or moderate CYP3A inhibitor. Food or drink containing grapefruit can inhibit CYP3A and should be avoided.⁷

Ivacaftor is a weak inhibitor of P-glycoprotein (P-gp) and elexacaftor inhibits uptake by OATP1B1/3 in vitro; serum concentrations of substrates of these transporters could increase if they are used concomitantly with the triple combination.

PREGNANCY AND LACTATION – There are no adequate studies on the use of elexacaftor, tezacaftor, or ivacaftor in pregnant women, and no animal reproduction studies with the 3 drugs administered concomitantly. No teratogenicity or adverse developmental outcomes were reported in pregnant animals exposed separately to elexacaftor, tezacaftor, or ivacaftor; decreased fetal body weights were observed in animals at doses that produced maternal exposures 1-5 times the exposure at the maximum recommended human dose.

In a survey of CFTR modulator use (ivacaftor alone or in combination with lumacaftor or tezacaftor) during pregnancy that included 35 women, 27 live births were reported (3 pregnancies resulted in miscarriages; 1 was terminated for maternal health concerns; 4 were ongoing in the final trimester). No treatment-related complications occurred in exposed infants, and no complications were reported in 5 infants exposed to CFTR modulators during breastfeeding.⁸
Elexacaftor, tezacaftor, and ivacaftor are excreted in the milk of lactating rats. Lumacaftor and ivacaftor have been detected in human breast milk.

**DOSAGE AND ADMINISTRATION — Trikafta** is available in fixed-dose tablets containing 100 mg of elexacaftor, 50 mg of tezacaftor, and 75 mg of ivacaftor copackaged with tablets containing 150 mg of ivacaftor alone. The recommended dosage is 2 combination tablets each morning followed by one ivacaftor tablet about 12 hours later. Each dose should be taken with fat-containing food.

Liver function tests should be evaluated before starting treatment, quarterly during the first year, and annually thereafter. In patients with moderate hepatic impairment (Child-Pugh B), **Trikafta** should be used with caution and at a reduced dose; the evening ivacaftor dose should be omitted. **Trikafta** should not be used in patients with severe hepatic impairment (Child-Pugh C).

**CONCLUSION —** Approval of **Trikafta** (not approved in Canada), a combination of the cystic fibrosis transmembrane conductance regulator (CFTR) modulators elexacaftor, tezacaftor, and ivacaftor, appears to be an important advance in the treatment of cystic fibrosis (CF). The combination significantly improved pulmonary function and reduced pulmonary exacerbations in CF patients ≥12 years old with a single Phe508del allele and was significantly more effective than tezacaftor/ivacaftor (**Symdeko**) in patients homozygous for the Phe508del mutation. About 90% of patients with CF can be treated with the triple combination. Only about 50-60% were eligible for treatment with lumacaftor/ivacaftor (**Orkambi**) and tezacaftor/ivacaftor. The efficacy and safety of **Trikafta** in children <12 years old with CF is under investigation. All CFTR modulators are very expensive and must be taken indefinitely.

1. Ivacaftor (Kalydeco) for cystic fibrosis. Med Lett Drugs Ther 2012; 54:29.

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**Corticosteroids in Community-Acquired Pneumonia**

Recently updated guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) address the use of corticosteroids as an adjunct to antimicrobials for treatment of community-acquired pneumonia (CAP).  

**CLINICAL STUDIES — Severe CAP** — Data showing a clinically significant mortality benefit of corticosteroids in the treatment of patients with severe CAP are limited. Some meta-analyses have found a reduced risk of death with corticosteroid use in such patients, but others have not, and the studies included in the meta-analyses varied in their quality and their definitions of severe CAP.

In one double-blind trial, 46 patients with severe CAP were randomized to receive IV hydrocortisone (200-mg bolus, then 10 mg/hr) or placebo for 7 days in addition to standard treatment. Treatment with hydrocortisone compared to placebo resulted in significantly shorter median durations of mechanical ventilation (4 vs 10 days) and hospital stay (13 vs 21 days). Seven patients in the placebo group died versus none in the hydrocortisone group.

Reductions in the durations of mechanical ventilation and hospital stay also occurred with use of IV hydrocortisone compared to placebo in a single-blind trial in 80 ICU patients with CAP, but baseline serum creatinine and blood urea nitrogen levels were higher in the placebo group. Chronic kidney disease is associated with an increased risk of pneumonia-related morbidity and mortality.

In another double-blind trial, 785 patients hospitalized with CAP were randomized to receive oral prednisone 50 mg or placebo once daily for 7 days. Time to clinical stability, the primary endpoint, was significantly shorter with prednisone than with placebo (3.0 vs 4.4 days), but prednisone did not significantly improve

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**Summary: Corticosteroids in CAP**

- Clinical trials evaluating whether adjunctive use of corticosteroids improves rates of morbidity and mortality in severe CAP have produced mixed results.
- There is no evidence that adjunctive use of corticosteroids improves outcomes in mild to moderate CAP.
- Corticosteroids increase the risk of hyperglycemia, and their use has been associated with increased rates of bleeding, secondary infection, and rehospitalization.
- Guidelines advise against adjunctive treatment of CAP or influenza pneumonia with corticosteroids except in patients with other indications for their use.
other clinical outcomes such as mortality rates and pneumonia recurrence, and it significantly increased the risk of hyperglycemia (19% vs 11%). Whether the difference in the primary endpoint shows a real beneficial effect of prednisone or is an artifact of its effects on certain markers of clinical stability (e.g., temperature, blood pressure) is unclear.10

In another double-blind trial, 120 patients with severe CAP and a high inflammatory response (C-reactive protein >150 mg/L) were randomized to receive IV methylprednisolone 0.5 mg/kg or placebo every 12 hours for 5 days. Treatment failure, the primary endpoint, occurred significantly less often with methylprednisolone than with placebo (13% vs 31%). This difference was primarily due to a lower rate of late radiographic progression with methylprednisolone than with placebo (13% vs 31%). This drug did not significantly reduce in-hospital mortality, time to clinical stability, or length of stay.11

Mild to Moderate CAP — There is no evidence that corticosteroids reduce mortality rates or other adverse clinical outcomes in patients with mild to moderate CAP. In a randomized, double-blind trial in 816 hospitalized patients with CAP of varying severity, a bundled intervention including use of prednisolone acetate 50 mg/day for 7 days did not improve length of stay, mortality rates, or readmission rates compared to standard treatment and was associated with an increased risk of GI bleeding (2.2% vs 0.7%).12

ADVERSE EFFECTS — Hyperglycemia occurs commonly with use of corticosteroids and can be clinically significant.13 Corticosteroids also have been associated with increased rates of bleeding, secondary infection, and rehospitalization.11,12,13 One meta-analysis found an increased risk of death with use of corticosteroids in small retrospective studies of patients with influenza pneumonia.14

GUIDELINES — The new ATS/IDSA guidelines advise against adjunctive corticosteroid treatment of CAP or influenza pneumonia except in patients who have other indications for their use, such as asthma, COPD, or an autoimmune disease. They do endorse the recommendation in current sepsis guidelines that IV hydrocortisone 200 mg/day be used in patients who have CAP with septic shock that is refractory to fluid resuscitation and vasopressor support, even though the sepsis guidelines classify this recommendation as weak and the quality of evidence supporting it as low.15

CONCLUSION — Data on whether adjunctive corticosteroids improve clinical outcomes in patients with severe community-acquired pneumonia (CAP) are mixed; until more evidence becomes available, they probably should not be used routinely, but they should be used in patients with refractory septic shock. Corticosteroids can cause clinically significant hyperglycemia. There are no data to support their use in the treatment of mild to moderate CAP.


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Upon completion of this activity, the participant will be able to:

1. Discuss the 2019-2020 recommendations for antiviral treatment and prophylaxis of seasonal influenza.

2. Review the efficacy and safety of eluxad证件/tezacafor/ivacafor (Trilkafa) for treatment of cystic fibrosis.

3. Discuss the role of adjunctive corticosteroid use in patients with community-acquired pneumonia.

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Questions on next page
### Antiviral Drugs for Influenza

1. Which of the following drugs is active against both influenza A and influenza B viruses?
   - a. oseltamivir
   - b. zanamivir
   - c. baloxavir
   - d. all of the above

2. Which of the following otherwise healthy persons is at high risk for complications of influenza?
   - a. a 4-year-old boy
   - b. a 15-year-old American Indian girl
   - c. a 68-year-old woman
   - d. all of the above

3. A 32-year-old pregnant woman presents with runny nose, cough, chills, and a temperature of 101°F. Physical examination indicates that she does not have pneumonia. She says that several of her coworkers have the flu. You should tell her that she should:
   - a. get a flu test
   - b. take 650 mg of acetaminophen and get some rest
   - c. take baloxavir
   - d. take oseltamivir

4. A 66-year-old man with COPD has had influenza symptoms for 4 days. He asks whether he should be treated with an antiviral drug. You should tell him that he should:
   - a. only be treated if his influenza test is positive
   - b. take zanamivir
   - c. take oseltamivir
   - d. not be treated with an antiviral drug because he has been sick for too long

5. Use of a neuraminidase inhibitor or baloxavir for treatment of uncomplicated influenza shortens the duration of symptoms by:
   - a. 12 hours
   - b. 24 hours
   - c. 36 hours
   - d. 48 hours

6. What percentage of recently circulating influenza viruses tested by the World Health Organization has been susceptible to neuraminidase inhibitors?
   - a. 60%
   - b. 70%
   - c. 80%
   - d. >99%

### Elexacaftor/Tezacaftor/Ivacaftor (Trikafta) for Cystic Fibrosis

7. What percentage of patients with cystic fibrosis has at least one copy of the Phe508del mutation and could potentially benefit from taking Trikafta?
   - a. 40%
   - b. 60%
   - c. 80%
   - d. 90%

8. Trikafta:
   - a. must be taken indefinitely
   - b. has improved pulmonary function and reduced pulmonary exacerbations in cystic fibrosis patients with a single Phe508del allele
   - c. should be taken with fat-containing food
   - d. all of the above

### Corticosteroids in Community-Acquired Pneumonia

9. Randomized, double-blind trials in patients with mild to moderate community-acquired pneumonia have found that corticosteroid treatment:
   - a. decreased mortality rates
   - b. reduced time to clinical stability
   - c. reduced the risk of treatment failure
   - d. none of the above

10. New American Thoracic Society/Infectious Disease Society of America guidelines do not recommend routine use of corticosteroids in patients with community-acquired or influenza pneumonia, except in:
    - a. those who have other indications for corticosteroid use
    - b. children <12 years old
    - c. those with severe hepatic impairment (Child-Pugh C)
    - d. all of the above