Antiviral Drugs for Seasonal Influenza 2015-2016

Antiviral drugs can be used for treatment of influenza and as an adjunct to influenza vaccination for prophylaxis. Frequently updated information on influenza activity and antiviral resistance is available from Health Canada, and the CDC at www.cdc.gov/flu.

INDICATIONS FOR TREATMENT — The CDC recommends antiviral treatment as soon as possible for all persons with suspected influenza who are at high risk for complications, including children <2 years old, persons <19 years old receiving long-term acetylsalicylic acid (aspirin in US) therapy, adults ≥65 years old, morbidly obese persons (BMI ≥40), women who are pregnant or ≤2 weeks postpartum, persons of American Indian/Alaska Native heritage, residents of nursing homes and other chronic care facilities, and persons of any age who have certain chronic medical conditions or are immunosuppressed. Antiviral treatment is also recommended for patients with suspected or confirmed influenza who show signs of clinical deterioration, develop symptoms of lower respiratory tract infection, or require hospitalization, and it can be considered for previously healthy persons with uncomplicated influenza if it can be started within 48 hours of symptom onset.

INDICATIONS FOR PROPHYLAXIS — Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to influenza. It can be considered for persons at high risk for complications who are unvaccinated or unlikely to respond to vaccination or have received influenza vaccine within the last 2 weeks, for unvaccinated healthcare workers who are exposed to influenza, and to help control outbreaks in nursing homes. When indicated, chemoprophylaxis should be started within 48 hours after exposure to the virus.

Table 1. Antiviral Drugs for Seasonal Influenza 2015-2016

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
<th>U.S. Cost¹</th>
<th>CAN Cost¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir – Tamiflu (Hoffman-La Roche; Genentech in US)</td>
<td>30, 45, 75 mg caps; 6 mg/mL oral susp</td>
<td>Prophylaxis: 75 mg PO once/d³</td>
<td>Prophylaxis: 30–75 mg PO once/d²</td>
<td>$131.50</td>
<td>$42.60</td>
</tr>
<tr>
<td></td>
<td>Treatment: 75 mg PO bid x 5 d⁴</td>
<td>Treatment: 30–75 mg PO bid x 5 d⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peramivir – Rapivab (Seqirus)</td>
<td>200 mg/20 mL single-use vials</td>
<td>Prophylaxis: Not approved</td>
<td>Treatment: 600 mg IV once²</td>
<td>950.00³</td>
<td>N.A.C.</td>
</tr>
<tr>
<td></td>
<td>Treatment: Not approved</td>
<td>Treatment: Not approved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanamivir – Relenza⁵ (GSK)</td>
<td>5 mg/blister for inhalation⁶</td>
<td>Prophylaxis: 2 inh once/d²</td>
<td>Prophylaxis¹: ≥5 yrs: 2 inh once/d²</td>
<td>59.00⁶</td>
<td>38.60</td>
</tr>
<tr>
<td></td>
<td>Treatment: 2 inh bid x 5d</td>
<td>Treatment: ≥7 yrs: 2 inh bid x 5d</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.A.C. = Not available in Canada

1. Approximate WAC for 5 days’ treatment at the adult dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. December 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy.

2. When indicated for post-exposure prophylaxis in households, a 10-day course is recommended. For prophylaxis of exposures in institutions, the drug should be taken for at least 1 week after the end of the outbreak. For prophylaxis during community outbreaks, oseltamivir has been shown to be effective and safe when taken for up to 42 days, and zanamivir for up to 28 days. Some expert clinicians would use twice-daily therapeutic doses for post-exposure prophylaxis in high-risk immunocompromised persons.

3. Dosage for patients with CrCl <30 mL/min: 30 mg once/d; CrCl 30–60 mL/min: 30 mg every other day; and stage renal disease on hemodialysis (HD): 30 mg after every other HD; continuous ambulatory peritoneal dialysis (CAPD): 30 mg once/wk immediately following exchange.

4. For children 1-12 yrs old; ≤15 kg: 30 mg; 15.1-33 kg: 45 mg; 33.1-40 kg: 60 mg; ≥40.1 kg: 75 mg. The FDA-approved dose for treatment of infants 2 weeks to less than 1 year old is 3 mg/kg bid. Although not Health Canada- or FDA-approved for prophylaxis for children <1 year old, the ACIP and CDC recommend that children 3-11 months old receive 3 mg/kg once/d.

5. Hospitalized, critically ill, or immunocompromised patients may be treated longer.

6. Dosage for patients with CrCl <30 mL/min: 30 mg bid; CrCl 30–60 mL/min: 30 mg once/d; and end-stage renal disease on hemodialysis (HD): 30 mg after every HD; continuous ambulatory peritoneal dialysis (CAPD): 30 mg immediately following exchange. Oseltamivir is not recommended for patients with end-stage renal disease on dialysis.

7. Dosage for patients with CrCl 30–49 mL/min: 200 mg IV once; CrCl 10–29 mL/min: 100 mg IV once; chronic renal impairment on hemodialysis: administer dose (based on renal function) after dialysis.

8. Approximate WAC for 3 single-use vials.

9. Not recommended for use in patients with underlying respiratory disease such as asthma or COPD or in patients with severe influenza.

10. Available in a carton containing 5 rotadisks (each rotadisk contains 4-5 mg blisters of the active drug in a lactose carrier) and a Diskhaler inhalation device. Zanamivir should not be used in a nebulizer. W zanamivir is available under an emergency investigational new drug request to the manufacturer for hospitalized patients with severe influenza (GSK 877-526-8019).

11. Approximate WAC for 5 days’ treatment at the adult dosage, based on prices from a national wholesaler (prices in Ontario, December 2015).

12. In Canada, recommended in children ≥7 years.
NEURAMINIDASE INHIBITORS — Neuraminidase inhibitors are currently the drugs of choice for treatment of influenza; most of the recently circulating influenza viruses tested by the CDC have been susceptible to these drugs. When used for chemoprophylaxis against susceptible strains of seasonal influenza A or B viruses, oseltamivir (Tamiflu) and zanamivir (Relenza) have generally been about 70-90% effective. Oseltamivir, which is taken orally, and zanamivir, which is inhaled, can be used for chemoprophylaxis or treatment of influenza in children and adults. Peramivir (Rapivab; not approved in Canada), which is administered intravenously as a single dose, is FDA-approved for treatment of uncomplicated influenza in adults; it appears to be similar in efficacy to oseltamivir.

Resistance — Resistance to oseltamivir or peramivir can emerge during or after treatment, especially in immunocompromised patients with prolonged viral shedding. Resistant isolates have remained susceptible to zanamivir.

Treatment Recommendations — Neuraminidase inhibitors can decrease the duration of fever and symptoms. They are most effective when started within 48 hours after symptom onset, but the results of some observational studies in hospitalized and critically ill patients suggest that starting treatment up to 4-5 days after symptoms appear can reduce the risk of complications such as pneumonia, respiratory failure, and death. The usual duration of treatment with oseltamivir or zanamivir is 5 days, but a longer treatment course of oseltamivir (e.g., 10 days) is often used for critically ill or immunocompromised patients, in whom viral replication may be protracted. Peramivir is given as a single dose for treatment of acute uncomplicated influenza.

No neuraminidase inhibitor is FDA-approved for use in hospitalized or critically ill patients. For such patients, the CDC recommends administering oseltamivir orally or by nasogastric tube and considering use of IV peramivir or investigational IV zanamivir (GSK: 877-626-8019) for those who cannot take oseltamivir.

Adverse Effects — Nausea, vomiting, and headache are the most common adverse effects of oseltamivir; taking the drug with food may improve its gastrointestinal tolerability. Bronchospasm can occur with inhaled zanamivir; the drug should not be used in patients with underlying airway disease. Neutropenia has occurred with peramivir. Neuropsychiatric events including self-injury and delirium, which can be a complication of influenza illness, have been reported in patients taking neuraminidase inhibitors, particularly children treated with oseltamivir.

Neuraminidase inhibitors administered within 48 hours before or <2 weeks after administration of the intranasal live-attenuated influenza vaccine (Flumist Quadrivalent) may interfere with the vaccine’s efficacy. Inactivated influenza vaccine can be given at any time relative to use of a neuraminidase inhibitor.

PREGNANCY — Pregnant women are at high risk for complications of influenza, including death. Even though all three neuraminidase inhibitors are classified as category C (some maternal and fetal toxicity in animals; no adequate studies in pregnant women) for use during pregnancy, prompt treatment with one of these antiviral drugs is recommended. Oseltamivir appears to be safe for use during pregnancy. Chemoprophylaxis can be considered for women who are pregnant or ≤2 weeks postpartum who have had close contact with someone likely to have been infected with influenza.

CONCLUSION — Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to influenza. A neuraminidase inhibitor, either oral oseltamivir (Tamiflu) or inhaled zanamivir (Relenza), is the drug of choice for treatment of patients with uncomplicated influenza. Oseltamivir is preferred for use in pregnant women and in patients with underlying airway disease. IV peramivir (Rapivab; not approved in Canada) is an option for patients who are unable to take oseltamivir or zanamivir.
Intravenous Diclofenac (Dyloject)

The FDA has approved Dyloject (Hospira; not approved in Canada), an IV formulation of the NSAID diclofenac sodium, for use in adults. It can be administered alone for treatment of mild to moderate pain or in combination with opioid analgesics for moderate to severe pain. Dyloject is the first injectable formulation of diclofenac to become available in the US.

NONOPIOIDS FOR PAIN — Use of an NSAID in addition to an opioid analgesic for management of postoperative pain has been shown to reduce opioid use and the incidence of opioid-related adverse effects. Administration of an oral drug may not be possible during or immediately after surgery. Injectable formulations of ketorolac and ibuprofen (Caldolor) are approved for treatment of pain; IV ibuprofen must be infused over 30 minutes. Use of ketorolac is limited to 5 days because of an increased risk of GI bleeding with longer use. Acetaminophen is available in an IV formulation (Ofirmev; not available in Canada) that is infused over 15 minutes; it is generally less opioid-sparing than NSAIDs, but it is not nephrototoxic and does not increase the risk of bleeding.1,3

THE NEW FORMULATION — Diclofenac has poor aqueous solubility. IV formulations of diclofenac are available outside the US, but they must be infused slowly to minimize venous irritation. Dyloject was developed by complexing diclofenac sodium with an inert solubility enhancer, hydroxypropyl-ß-cyclodextrin (HPßCD), that releases diclofenac immediately upon injection. Following IV bolus administration, peak serum concentrations of Dyloject are achieved within 5 minutes, compared to about 1.5 hours with oral diclofenac potassium, and maximum concentrations are about 4.8-fold higher than those with the oral formulation.4

CLINICAL STUDIES — Approval of Dyloject was based on the results of two randomized, double-blind, placebo- and active-controlled, short-term trials in >600 adults with moderate to severe postoperative pain.

In one trial in patients who had undergone abdominal or pelvic surgery, those who received an IV bolus of diclofenac 37.5 mg or ketorolac 30 mg every 6 hours starting within 6 hours after surgery had similar reductions in pain intensity during the 48-hour interval following administration of the first dose, the primary endpoint, and both active drugs were significantly more effective than placebo. A >30% reduction in pain intensity during the first 6-hour dosing period occurred in 69.8% of patients receiving diclofenac 37.5 mg and in 76.8% of those receiving ketorolac 30 mg, compared to 55.3% with placebo. Patients receiving the active treatments required significantly less rescue IV morphine (total cumulative dose from 0–72 hours after surgery was 7.4 mg for diclofenac 37.5 mg and 8.5 mg for ketorolac 30 mg vs 15.9 mg for placebo).5

In the other trial, patients with pain following elective orthopedic surgery generally had similar mean pain intensity scores with IV diclofenac (18.75, 37.5, or 50 mg)
or IV ketorolac (15 or 30 mg) given every 6 hours for up to 5 days; scores with both active drugs were superior to those with placebo for all scheduled assessments from 6 to 120 hours after treatment initiation. The onset of analgesia was faster with diclofenac than with ketorolac (a mean of 10 vs 30 minutes). A ≥30% reduction in pain intensity occurred in 81% of the patients receiving diclofenac and in 75% of those receiving ketorolac, versus 43% of those given placebo. Patients receiving diclofenac used significantly less supplemental morphine over 5 days of treatment than those receiving ketorolac (11.8 vs 18.1 mg). In patients aged 65 years old given low doses of the active drugs, diclofenac was significantly more effective than ketorolac.6

ADVERSE EFFECTS — In clinical trials, infusion site pain and extravasation were more common with diclofenac than with placebo (10% and 3%, respectively, vs 8% and 1%). GI adverse effects, including ulceration, perforation, and bleeding, can occur with any NSAID, but bleeding-related adverse effects were not more common with diclofenac than with placebo in the short-term trials. An increased risk of serious cardiovascular thrombotic events such as myocardial infarction or stroke has been reported with some NSAIDs; the risk appears to be highest with diclofenac.7 There was no evidence of an increased risk of serious cardiovascular thrombotic events such as myocardial infarction or stroke has been reported with any NSAID, but bleeding-related adverse effects were not more common with diclofenac than with placebo (10% and 3%, respectively, vs 8% and 1%). GI adverse effects, including ulceration, perforation, and bleeding, can occur with any NSAID, but bleeding-related adverse effects were not more common with diclofenac than with placebo for all scheduled assessments from 6 to 120 hours after treatment initiation. The onset of analgesia was faster with diclofenac than with ketorolac (a mean of 10 vs 30 minutes). A ≥30% reduction in pain intensity occurred in 81% of the patients receiving diclofenac and in 75% of those receiving ketorolac, versus 43% of those given placebo. Patients receiving diclofenac used significantly less supplemental morphine over 5 days of treatment than those receiving ketorolac (11.8 vs 18.1 mg). In patients aged 65 years old given low doses of the active drugs, diclofenac was significantly more effective than ketorolac.6

All NSAIDs inhibit renal prostaglandins and decrease renal blood flow. In clinical trials, acute renal decompensation occurred in 4% of patients with renal impairment treated with Dylorocet; it should not be used in patients who are dehydrated or have moderate to severe renal impairment. NSAIDs frequently cause small increases in aminotransferase activity; serious hepatotoxicity is rare, but may occur more frequently with diclofenac. Dylorocet is not recommended for patients with moderate to severe hepatic impairment.

DRUG INTERACTIONS — Diclofenac is metabolized primarily by CYP2C9; concomitant use with CYP2C9 inhibitors may increase its serum concentrations and toxicity and use with CYP2C9 inducers may decrease its efficacy.8 Like other NSAIDs, diclofenac may decrease the effectiveness of diuretics, beta blockers, ACE inhibitors, and some other antihypertensive drugs, may increase the toxicity of lithium, methotrexate, and cyclosporine, and may increase the risk of gastrointestinal bleeding in patients taking anticoagulants.

DOSAGE AND ADMINISTRATION — Dylorocet is supplied in single-dose vials containing 37.5 mg of diclofenac sodium per mL. The recommended dosage is 37.5 mg administered by IV bolus injection over 15 seconds every 6 hours as needed. The total daily dose should not exceed 150 mg.

CONCLUSION — The new IV formulation of diclofenac sodium (Dylorocet; not approved in Canada) relieves postsurgical pain in adults, has an opioid-sparing effect, and is generally well tolerated. It acts more rapidly, but is otherwise similar in efficacy to IV ketorolac, which costs much less. Acetaminophen is less opioid-sparing than an NSAID, but it is probably safer.


Empagliflozin/Metformin (Synjardy) for Type 2 Diabetes

The FDA has approved Synjardy (Boehringer Ingelheim/Lilly; not approved in Canada), a fixed-dose combination of the sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin (Jardiance) and metformin (Glucophage, and others), for treatment of patients with type 2 diabetes not adequately controlled on either of these drugs alone or already being treated with both empagliflozin and metformin. It is the third SGLT2 inhibitor/metformin combination to be approved in the US (SGLT2 inhibitors are not approved in combination with metformin in Canada).1

Empagliflozin: em” pa gli floe’ zin Synjardy: sin jar’ dee

STANDARD TREATMENT — Used alone, oral antihyperglycemic drugs generally lower glycated hemoglobin (HbA1c) by 0.5–1.5%. Metformin is the preferred first-line treatment for type 2 diabetes, but most patients
eventually require multi-drug therapy or insulin to achieve glycemic control. There is no consensus on which drug(s) should be added to metformin, which is available in fixed-dose combinations with many other antihyperglycemic drugs.

**MECHANISM OF ACTION —** Metformin decreases hepatic glucose production and, to a lesser extent, increases peripheral glucose uptake. Empagliflozin decreases renal tubular reabsorption of glucose (and sodium) and increases urinary glucose excretion.

**CLINICAL STUDIES —** No new clinical studies were required for approval of the combination, which has been shown to be bioequivalent to the individual tablets of metformin and empagliflozin taken together. In randomized, double-blind trials in patients who had not achieved glycemic goals with metformin alone, addition of empagliflozin lowered HbA1c by an additional 0.7–0.8%. Treatment with empagliflozin has also resulted in reductions in systolic blood pressure and weight.

An Empagliflozin Cardiovascular Study — A randomized, double-blind trial in 7020 patients with type 2 diabetes and established cardiovascular disease (prior myocardial infarction or stroke or angiographically demonstrated obstruction) found a significant reduction in cardiovascular mortality with use of empagliflozin. The mechanism of this reduction is unclear and it is not known whether other SGLT2 inhibitors have a similar effect. These results may not apply to patients with type 2 diabetes and less advanced cardiovascular disease.

**ADVERSE EFFECTS —** Metformin commonly causes gastrointestinal adverse effects (metallic taste, nausea, abdominal pain, diarrhea), which can be minimized by starting with a low dose, titrating slowly, dividing doses, and taking the drug with food. Lactic acidosis can occur with accumulation of metformin; patients with renal impairment are at greatest risk. Decreases in vitamin B12 serum concentrations have occurred in patients taking metformin long-term and have rarely been associated with anemia.

Empagliflozin can cause genital mycotic infections and urinary tract infections in both men and women, some of which have been serious (urosepsis and pyelonephritis). It has a diuretic effect, which can lead to dehydration, hypovolemia, and hypotension, particularly in elderly patients with renal dysfunction and in those taking loop diuretics. Modest increases in serum creatinine and LDL cholesterol can occur. Ketoacidosis has been reported with use of SGLT2 inhibitors.

**PREGNANCY —** Synjardy is classified as category C (developmental toxicity in animals; no adequate studies in women) for use during pregnancy.
**Drug Interactions** — Hypoglycemia can occur if Synjardy is taken with insulin or a sulfonylurea; a reduction in the dosage of the coadministered drug may be needed. Concurrent use of Synjardy and a diuretic can increase the risk of volume depletion.

**Dosage and Administration** — Synjardy should be taken twice daily with meals. The recommended dosage is based on the current dose of empagliflozin and/or metformin. In patients already taking metformin, the starting dose of Synjardy should be empagliflozin 5 mg plus their current daily dose of metformin. In those already taking empagliflozin, the initial Synjardy dose should be metformin 500 mg with their current daily dose of empagliflozin. The maximum daily dose is 2000 mg of metformin and 25 mg of empagliflozin.

The combination should not be used in men with serum creatinine levels ≥1.5 mg/dL, women with serum creatinine levels ≥1.4 mg/dL, or patients with an eGFR <45 mL/min/1.73 m².

**Conclusion** — The fixed-dose combination of empagliflozin and metformin (Synjardy; not approved in Canada) would be more convenient than taking the same drugs separately, but adding empagliflozin to metformin has only a modest effect on HbA1c. A significant decrease in cardiovascular mortality has been reported with use of empagliflozin (Jardiance) in patients with type 2 diabetes who have established cardiovascular disease, but the long-term safety of SGLT2 inhibitors is still unknown.

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**References**


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**In Brief**

**Oral Phenylephrine for Nasal Congestion**

In 2007, an FDA advisory committee asked that placebo-controlled, dose-ranging trials be conducted to establish the efficacy of the oral decongestant phenylephrine (Sudafed PE, and others; not available in Canada), which is sold over the counter (OTC) as a single agent and in combination with other drugs for treatment of cold and allergy symptoms. Phenylephrine replaced pseudoephedrine (Sudafed, and others) in many OTC formulations when access to pseudoephedrine-containing products was restricted in an effort to reduce their use in the synthesis of methamphetamine.

**Clinical Studies** — In a randomized, open-label, dose-ranging trial in 539 patients with seasonal allergic rhinitis, phenylephrine doses up to four times the recommended dose of 10 mg were no more effective than placebo in reducing symptomatic nasal congestion.1 Other recent studies have also found oral phenylephrine no more effective than placebo in reducing nasal congestion.2,4

**Alternatives** — Oral pseudoephedrine reduces nasal congestion, but has no effect on other symptoms such as sneezing, itching, or rhinitis, and tolerance to its effects can occur with repeated use. Potential adverse effects include insomnia, excitability, headache, nervousness, anorexia, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention. Pseudoephedrine should be used cautiously in patients with cardiovascular disease, hypertension, diabetes, hyperthyroidism, narrow-angle glaucoma, or bladder neck obstruction.

**Intranasal Decongestants** such as oxymetazoline (Dristan, and others; Afrin, and others in US) are effective and less likely than pseudo-ephedrine to cause systemic adverse effects, but they can cause stinging, burning, sneezing, dryness of the nose and throat, and, if used for more than 3–5 consecutive days, rebound congestion (rhinitis medicamentosa). Intranasal corticosteroids are the most effective drugs available for prevention and relief of nasal congestion and other seasonal allergic rhinitis symptoms.5

**Conclusion** — Oral phenylephrine is not effective for treatment of nasal congestion.
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Upon completion of this program, the participant will be able to:
1. Discuss the 2015-2016 recommendations for use of antiviral drugs for prophylaxis and treatment of seasonal influenza.
2. Review the efficacy and safety of the new intravenous formulation of diclofenac (Dyloject) for management of pain in adults.
3. Review the efficacy and safety of empagliflozin/metformin (Synjardy) for treatment of type 2 diabetes.
4. Discuss the efficacy of the oral decongestant phenylephrine (Sudafed PE, and others) for treatment of cold and allergy symptoms.

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Questions start on next page
### Antiviral Drugs for Seasonal Influenza 2015-2016

1. Antiviral treatment is recommended for which of the following with suspected influenza?
   - a. adults >65 years old
   - b. residents of nursing homes
   - c. immunosuppressed patients
   - d. all of the above

2. Neuraminidase inhibitors are most effective for treatment of influenza when started how long after symptom onset?
   - a. within 48 hours
   - b. within 72 hours
   - c. within 96 hours
   - d. within 5 days

3. A 28-year-old woman in her fourth month of pregnancy was exposed to family members with documented influenza and has had influenza-like symptoms for one day. When you suggest treatment with an antiviral drug, she asks whether the drug could hurt her baby. You could tell her that:
   - a. pregnant women are at high risk for complications of influenza
   - b. oseltamivir appears to be safe for use during pregnancy
   - c. no adequate studies of oseltamivir have been done in pregnant women
   - d. all of the above

### Intravenous Diclofenac (Dyloject)

4. IV diclofenac administered postoperatively has been shown to be:
   - a. noninferior to morphine
   - b. opioid-sparing
   - c. less effective than IV acetaminophen
   - d. safe in patients with renal impairment

5. Compared to IV ketorolac, IV diclofenac is:
   - a. similar in efficacy
   - b. less likely to be prothrombotic
   - c. less likely to cause nephrotoxicity
   - d. all of the above

### Diclofenac may decrease the effectiveness of:

6. Diclofenac may decrease the effectiveness of:
   - a. diuretics
   - b. fluoroquinolone antibiotics
   - c. glucocorticoids
   - d. all of the above

### Empagliflozin/Metformin (Syndardy) for Type 2 Diabetes

7. A 61-year-old man with type 2 diabetes well controlled on monotherapy with metformin has read about the reduction in cardiovascular mortality with empagliflozin and asks whether he could start taking the new combination. You could tell him that:
   - a. the reduced mortality with empagliflozin was only demonstrated in patients with established cardiovascular disease
   - b. empagliflozin can cause genitourinary tract infections in men and women
   - c. SGLT2 inhibitors like empagliflozin can cause ketoacidosis
   - d. all of the above

8. In clinical trials in patients who had not achieved glycemic goals with metformin alone, addition of empagliflozin lowered 
   HbA1c by about:
   - a. 0.4-0.5%
   - b. 0.7-0.8%
   - c. 0.9-1.0%
   - d. 1.2-1.3%

9. Metformin commonly causes:
   - a. hepatotoxicity
   - b. nephrotoxicity
   - c. gastrointestinal adverse effects
   - d. muscle cramps

### Oral Phenylephrine for Nasal Congestion

10. The most effective drug for treatment of seasonal allergic rhinitis symptoms is:
    - a. oral phenylephrine
    - b. an oral antihistamine
    - c. an intranasal antihistamine
    - d. an intranasal corticosteroid