Goal. The goal of this lesson is to provide information on boceprevir (Victrelis™), telaprevir (Incivek™), and rilpivirine (Edurant™).

Objectives. At the conclusion of this lesson, successful participants should be able to:
1. identify the new drugs by generic name, trade name and chemical name when relevant;
2. select the indication(s), pharmacologic action(s) and clinical applications for each drug;
3. recognize important therapeutic uses for the drugs and their applications in specified pathologies; and
4. demonstrate an understanding of adverse effects and toxicity, significant drug-drug interactions, and patient counseling information for these drugs.

Drugs discussed within this lesson are new molecular entity antivirals (Table 1) indicated to treat HIV-1 or hepatitis C viral infections. The lesson provides an introduction to the new drugs and is not intended to extend beyond a brief overview of the topic. The reader is, therefore, urged to consult the products’ Prescribing Information leaflet or Medication Guide, and other published reference sources for detailed descriptions.

### Hepatitis C
The World Health Organization has declared hepatitis C virus (HCV) infection a global health problem, citing an estimated 130 to 170 million people chronically infected worldwide, with three to four million individuals newly infected each year. Recent figures from the U.S. Centers for Disease Control and Prevention report that 3.2 million Americans are chronically infected with HCV, and approximately 10,000 die annually as a result of this persistent pathology. It is estimated that up to 20 percent of HCV-infected persons will develop complications of their liver disease, including fluid accumulation in the abdomen, jaundice (yellowish eyes or skin), infections, cirrhosis, end-stage liver disease and hepatocellular carcinoma. The mortality rate after cirrhosis has developed is 2 to 5 percent per year. End-stage liver disease due to HCV infection currently represents the major indication for liver transplantation in the Western world.

HCV is a single-stranded RNA virus that replicates by transcription of its genomic RNA. The viral nonstructural enzymes, NS3 and NS4A, are responsible for the proteolytic cleavage of the polyprotein to yield NS3 protease and NS4A. The NS3 protease is crucial for viral replication. The enzyme contains two different catalytic domains, a serine protease and an aspartate-dependent cysteine protease, which can be targeted with antivirals for treatment of chronic hepatitis C.

### Table 1
Selected new antiviral drugs

<table>
<thead>
<tr>
<th>Generic (Proprietary Name)</th>
<th>Applicant/Sponsor/Distributor</th>
<th>Indication</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (Victrelis)</td>
<td>Merck &amp; Co., Inc.</td>
<td>NS3/4A protease inhibitor for treatment of chronic hepatitis C</td>
<td>200 mg capsules</td>
</tr>
<tr>
<td>Rilpivirine (Edurant)</td>
<td>Tibotec Pharmaceuticals</td>
<td>HIV-1 specific non-nucleoside reverse transcriptase inhibitor for treatment of HIV-1 infection</td>
<td>25 mg tablets</td>
</tr>
<tr>
<td>Telaprevir (Incivek)</td>
<td>Vertex Pharmaceuticals</td>
<td>NS3/4A protease inhibitor for treatment of chronic hepatitis C</td>
<td>375 mg tablets</td>
</tr>
</tbody>
</table>
Therapeutic Management.
Management of chronic HCV infection should be individualized. Methods for prevention of transmission and the importance of adherence to treatment protocol should be stressed. Treatment is strongly recommended and should be considered in patients with chronic HCV infection and detectable levels of HCV RNA, elevated aminotransferase levels, and histologic evidence of progressive liver disease. The primary goals of therapy are to prevent complications and death from HCV, while reducing adverse events and maintaining quality of life. The difficulty in achieving these goals is complicated by the slow progression of chronic disease and treatment responses that are based on secondary findings versus long-term clinical outcomes.

Treatment History. The current therapeutic profile for management of hepatitis C infection was inaugurated almost 25 years ago following a small trial of recombinant human interferon alfa. The rationale for using interferon was based upon its broad antiviral effects and suspicion that it might be active against the still unrecognized agent of non-A, non-B hepatitis. Interferon showed striking effects, lowering serum aminotransferase levels and, in a proportion of patients, inducing lasting improvement in serum enzyme levels. It wasn’t until the hepatitis C virus was identified that the effects of interferon were understood. Interferon resulted in a decrease in HCV RNA levels, which led to a sustained absence of virus in some patients. The problem was that interferon required parenteral injections, had multiple adverse effects, and resulted in a poor overall response rate. Nonetheless, interferon was approved for use for hepatitis C management in the United States in 1992.

The next advance came with use of ribavirin (Copegus, Rebetol). Ribavirin is a nucleoside analogue that exerts activity against several flaviviruses. When HCV was identified as a flavivirus, ribavirin was an obvious treatment choice. Having little effect on serum HCV RNA levels, ribavirin led to improvements in aminotransferase levels and histologic characteristics of the liver. More importantly, when combined with interferon, ribavirin increased the rate of sustained virologic response (i.e., infection was no longer detected in the blood). Interferon plus ribavirin given in combination for 48 weeks yielded rates of sustained virologic response of 40 to 50 percent, two to three times the benefit obtained with interferon alone. Ribavirin was thus approved for use as an adjunct to interferon therapy of hepatitis C in 1998.

The third advance in therapy followed soon thereafter, with introduction of pegylated forms of interferon (peginterferon alfa; Pegasys, Peginteron) that allowed for once-weekly, rather than thrice-weekly, injections. Peginterferon yielded enhanced rates of sustained virologic response compared to standard interferon, 45 to 55 percent after a 48-week course of therapy with peginterferon and ribavirin. The response rates varied according to HCV genotype. Among patients infected with genotypes 2 and 3 (approximately 25 percent of patients in the United States), rates of sustained virologic response with a 24-week course and reduced doses of ribavirin were 70 to 80 percent. Rates of sustained virologic response among patients infected with genotype 1 (approximately 70 percent of U.S. patients) were less satisfactory, ranging from 40 to 50 percent and requiring 48 weeks of full dosing with ribavirin. In some persons, response rates were even lower, with rates of approximately 25 to 30 percent among African Americans. Increasing doses and length of therapy increased rates of sustained virologic response minimally and usually were associated with increased adverse effects. Peginterferon was approved in the United States in 2001.

It would be another decade.
before a fourth advance in hepatitis C therapy would be noted: approval of Incivek and VICTRELIS in 2011. With approval of these new drugs, there are now two additional treatment options for hepatitis C that offer a greater chance at a cure for some patients with this serious infection. The availability of these new therapies that significantly increase responses while potentially decreasing the overall duration of treatment is a major step forward in the battle against HCV.

Efforts toward developing new compounds against HCV have been hampered by difficulties in replicating the virus in cell culture and the lack of suitable animal models. Recent advances in the understanding of the HCV genome organization and life cycle, along with development of HCV replicons (a DNA or RNA molecule, or region of RNA that replicates from a single origin) and infectious viral particles in tissue culture systems have supported the rational design of agents that specifically inhibit HCV replication. The goal of future therapy for HCV is to develop antiviral drugs that are less toxic, more potent, and allow an even shorter duration of therapy than the current (i.e., before approval of the two new drugs) standard of care. Ideally, with these compounds, 12 to 24 weeks of therapy should be sufficient to cure most patients who have chronic HCV infection.

Telaprevir (Incivek) Safety and effectiveness of Incivek (in-SEE-veck) was shown in three Phase 3 clinical trials involving about 2,250 adult patients who were previously naive (untreated), or who had received prior therapy. In all studies, patients also received the drug along with peginterferon alfa and ribavirin. In previously untreated patients, 70 percent of those receiving Incivek experienced a sustained virologic response compared to standard treatment alone. The sustained virologic response for patients receiving Incivek across all studies, and across all patient groups, was between 20 and 45 percent higher than with the current standard of care – peginterferon plus ribavirin.

The studies indicated that treatment duration with Incivek can be shortened from 48 weeks to 24 weeks in most patients. Sixty percent of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care duration of 48 weeks). The sustained virologic response for those patients was 90 percent.

**Indications and Use.** Incivek is indicated for treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have been previously treated with interferon-based treatment, including prior non-responders, partial responders, and those who relapse. The new drug must only be used in combination with peginterferon alfa and ribavirin. Efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes Incivek or other HCV NS3/4A protease inhibitors (see Mechanism of Action).

**Mechanism of Action.** Telaprevir is an inhibitor of HCV NS3/4A serine protease, an enzyme necessary for the proteolytic cleavage of HCV-encoded polyprotein into mature proteins. The enzyme is, thus, essential for viral replication.

**Adverse Effects.** In clinical trials, the most common adverse drug reactions to Incivek (incidence at least 5 percent higher with Incivek than in controls) were rash, itching, anemia, dysgeusia (diminished sense of taste), hemorrhoids, anal itching and discomfort, fatigue, nausea and vomiting.

**Warnings, Precautions and Contraindications.** The following warnings and precautions are listed:

- **Pregnancy:** Incivek must be used in combination with peginterferon alfa and ribavirin. Ribavirin may cause birth defects and fetal death, so pregnancy in female patients and male partners of female patients should be avoided. Patients must have a negative pregnancy test prior to initiating therapy, at least two effective methods of contraception must be used, and monthly pregnancy tests obtained.

- **Serious skin reactions:** Serious skin reactions including drug rash with eosinophilia and systemic symptoms and Stevens-Johnson Syndrome have been reported. For serious skin reactions, all components of Incivek combination treatment should be discontinued immediately.

- **Rash:** Patients with mild to moderate rash should be monitored for progression. If rash progresses and becomes severe, Incivek should be discontinued.

- **Anemia:** Hemoglobin levels should be monitored prior to and at regular intervals during Incivek combination treatment. Dose modifications for ribavirin should be followed, and Incivek discontinued if required.

**Contraindications** include:

- All contraindications to peginterferon alfa and ribavirin also apply.

- Pregnant women and men whose female partners are pregnant: (see Warnings and Precautions).

- Co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events; and with drugs that strongly induce CYP3A, which may lead to lower exposure and loss of efficacy of Incivek. The Medication Guide lists drugs and herbal remedies that are contraindicated with Incivek.

**Drug Interactions.** (See Warnings, Precautions and Contraindications.)

**Dosage and Availability.** Incivek is taken in doses of 750 mg three times a day (seven to nine hours apart) with food (not low fat). The drug must be administered with both peginterferon alfa and ribavirin for all patients for
Table 2
Major counseling points for Incivek (telaprevir)*

This medicine is used with peginterferon alfa and ribavirin to treat chronic hepatitis C infections.
- Read the Medication Guide before you start taking Incivek and each time you get a refill.
- Tell your doctor:
  - if you are pregnant or may become pregnant, or are a male with a sexual partner who is pregnant.
  - if you develop a rash or other skin reaction;
- about all other prescription and nonprescription (OTC) medicines, vitamin/mineral supplements, natural products and herbal remedies you are taking. The Medication Guide has a list of medicines you should not take with Incivek.
- Periodic laboratory tests are important with this medicine. Be sure to make all testing appointments.
- Females and males must use 2 forms of effective birth control during treatment and for 6 months afterward. Hormonal contraceptives may not be reliable during Incivek therapy.
- Incivek must be taken with food. The dose is 1 tablet 3 times daily, in doses 7 to 9 hours apart, within 30 minutes of a meal or snack that contains about 20 grams of fat.
- Examples of foods like this are: a bagel with cream cheese; one-half cup of nuts; 3 tablespoonfuls of peanut butter; 1 cup of ice cream; 3 ounces of American or cheddar cheese; 2 ounces of potato chips; and one-half cup of trail mix.
- Do not stop taking Incivek or the other 2 medicines without first consulting your doctor.
- Do not use after the expiration date on the label. Properly discard unused medication.

*Excerpted from the FDA-approved Medication Guide

Boceprevir (Victrelis)
Safety and effectiveness of Victrelis (vic-TREL-is) were evaluated in two Phase 3 clinical trials involving nearly 1,500 adult patients. In both trials, two-thirds of the patients receiving Victrelis in combination with peginterferon alfa and ribavirin experienced a significantly increased and sustained virologic response, compared to peginterferon alfa and ribavirin alone.

Indications and Use. Like Incivek, Victrelis is a hepatitis C virus NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C genotype 1 infection. It must be administered in combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

Mechanism of Action. The drug is a direct-acting inhibitor of the HCV NS3/4A protease that is necessary for the proteolytic cleavage of HCV encoded polyprotein into mature proteins.

Adverse Effects. The most commonly reported adverse reactions (> than 35 percent of subjects) in clinical trials with adult subjects receiving the combination of Victrelis with peginterferon alfa and ribavirin were fatigue, anemia, nausea, headache and dysgeusia.

Warnings, Precautions and Contraindications. The following warnings and precautions are listed:
- Ribavirin may cause birth defects and fetal death: Pregnancy should be avoided in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy, must use two or more forms of contraception, and have monthly pregnancy tests performed.
- Anemia: The addition of Victrelis to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations compared with peginterferon alfa and ribavirin alone.
  - Neutropenia: The addition of Victrelis to peginterferon alfa and ribavirin may result in worsening of neutropenia associated with peginterferon alfa and ribavirin therapy alone.
- Contraindications include:
  - All contraindications to peginterferon alfa and ribavirin also apply to Victrelis since the new drug must be administered with peginterferon alfa and ribavirin.
  - Ribavirin may cause birth defects and fetal death (see Warnings and Precautions).

Drug Interactions. (See Warnings, Precautions and Contraindications.)

Dosage and Availability.
Doses of 800 mg (four capsules) orally are taken three times daily (every seven to nine hours) with a meal or light snack.

Victrelis is available as capsules containing 200 mg boceprevir.

Patient Information. Excerpts from the FDA-approved Medication Guide are presented in Table 3.

HIV/AIDS
Over the years, enhanced understanding of the pathophysiologic consequences of human immunodeficiency virus (HIV) infection has led to significant improvements in the clinical management of this infection. Life expectancies associated with the infection have
increased in most industrialized nations, and the rate of progression to acquired immunodeficiency syndrome (AIDS) has decreased. Little progress has been made, however, in terms of completely eradicating the virus. In areas where access to effective antiretrovirals is limited, mortality rates from HIV or AIDS remain high. National HIV transmission rates have also remained generally unchanged in most at-risk groups, with increases being noted in some subpopulations (e.g., African Americans, women). Global rates of infection remain high, with approximately four million new HIV infections reported annually.

With these points in mind, many researchers continue to emphasize prevention strategies that might reduce the severity of the epidemic worldwide. One such approach to disease prevention is the concept of preexposure prophylaxis. This involves the use of antiretrovirals either continuously or just immediately before high-risk situations, such as perinatal and occupational exposure to HIV to reduce the likelihood of successful HIV infection. Preexposure prophylaxis differs from postexposure prophylaxis, which involves the use of antiretrovirals immediately after a high-risk exposure. The concept of preexposure prophylaxis is controversial and involves several important concerns such as the potential to administer antiretrovirals to individuals not infected with HIV and the implications of high-risk behaviors.

It’s an established fact that systemic infection does not occur immediately after exposure, but is likely delayed for one to three days. During this period after exposure, a small population of “founder cells” appear to be responsible for the spread of infection to clusters of nearby cells, thereby expanding viral dissemination until a sustained secondary infection is achieved. Generally, virus can be recovered from antigen-presenting cells in the mucosa within 24 hours of viral exposure and regional lymph nodes within 48 to 72 hours. Viremia (presence of virus in the blood) is generally detectable as early as five days after initial acquisition. Administration of antiretroviral therapy during this window of opportunity when populations of founder cells are being established may disrupt the infection cycle to thereby aid the immune system in potentially eradicating the virus.

**Rilpivirine (Edurant)**

Safety and effectiveness of Edurant (ee-DUR-ant) is based on 48-week data from two Phase 3 clinical trials with 1,368 adult subjects with HIV infection, and from a 96-week (with extension to 192-week) trial. Patients had not received prior HIV therapy and were selected to receive treatment with Edurant or efavirenz (Sustiva), another non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of HIV infection. Both drugs were given in combination with other antiretroviral drugs. The new drug was as effective as efavirenz in lowering viral load. In the Edurant and efavirenz groups, 83 percent and 80 percent of subjects, respectively, had undetectable amounts of HIV in the blood after 48 weeks of treatment. Patients receiving rilpivirine who had a higher viral load at the onset of therapy were more likely not to respond to the drug than were patients with a lower viral load. Moreover, persons who failed therapy with rilpivirine developed more drug resistance than patients who failed efavirenz.

**Indications and Use.**

Edurant is a human immunodeficiency virus type 1 (HIV-1) specific NNRTI indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naive adult patients. The new drug does not cure HIV infection. Patients must remain on continuous HIV therapy to control HIV infection and decrease HIV-related illness.

**Mechanism of Action.**

Rilpivirine is an antiviral drug that inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase. Rilpivirine does not inhibit the human cellular DNA polymerases alfa, beta, and gamma.

**Adverse Effects.** The most common adverse drug reactions to Edurant (incidence >2 percent) of at least moderate to severe intensity (≥ Grade 2) were depression, insomnia, headache and rash.

**Warnings, Precautions and Contraindications.** The following warnings and precautions are listed:

- Caution should be given to prescribing Edurant with drugs that may reduce the exposure of
riclovirine (see Drug Interactions).

- Caution needs to be given to prescribing Edurant with drugs with a known risk of Torsade de Pointes.

- *Depressive disorders:* Severe depressive disorders (depressed mood, depression, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported. Immediate medical evaluation is recommended for severe depressive disorders.

- Patients may develop redistribution/accumulation of body fat or immune reconstitution syndrome.

**Contraindication** to Edurant: The drug should not be co-adminis-

**Drug Interactions.** Edurant should not be used in combination with NNRTIs. Co-administration of NNRTIs can inhibit CYP3A4, which may affect the plasma concentrations of rilpivirine. Co-administration with drugs that increase gastric pH may decrease plasma concentrations. A statement to patients and healthcare providers is included on the product’s label: ALERT: Find out about medicines that should NOT be taken with Edurant from your healthcare provider. A Patient Package Insert for Edurant is available for patient information.

**Dosage and Availability.** Edurant is taken in doses of 25 mg (one 25 mg tablet) once daily with a meal.

Edurant is available as tablets containing 25 mg rilpivirine.

**Patient Information.** Excerpts of the FDA-approved Patient Information are shown in Table 4.

**Overview and Summary**

Infection with the virus that causes hepatitis C or acquired human immunodeficiency syndrome is a serious event. Both infections are associated with high morbidity and mortality. With approval of two new drugs to treat hepatitis C and another to treat HIV/AIDS, patients now have additional treatment options.

---

**Table 4**

<table>
<thead>
<tr>
<th>Major counseling points for Edurant (rilpivirine)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>This medicine is used with other medicines to treat HIV (Human Immunodeficiency Virus) infection.</td>
</tr>
<tr>
<td>- Read the Patient Information before you start taking Edurant and each time you get a refill.</td>
</tr>
<tr>
<td>- Tell your doctor:</td>
</tr>
<tr>
<td>- if you have liver problems, mental health problems or a heart condition called Torsade de Pointes;</td>
</tr>
<tr>
<td>- if you feel sad or hopeless, anxious or depressed, or have thoughts of hurting yourself;</td>
</tr>
<tr>
<td>- about all other prescription and nonprescription (OTC) medicines, vitamin/mineral supplements, natural products and herbal remedies you are taking. The Patient Information has a list of medicines you should not take with Edurant.</td>
</tr>
<tr>
<td>- Periodic laboratory testing is important with this medicine. Be sure to make all testing appointments.</td>
</tr>
<tr>
<td>- WOMEN: Notify your doctor if you become or intend to become pregnant, or are breastfeeding.</td>
</tr>
<tr>
<td>- Edurant is usually taken once daily with a meal. Do not change the dose or stop taking Edurant without first consulting your doctor.</td>
</tr>
<tr>
<td>- Store Edurant at room temperature in its original container to protect it from light. Do not use after the expiration date on the label. Properly discard unused medication.</td>
</tr>
</tbody>
</table>

* Excerpted from the FDA-approved Patient Information.
continuing education quiz

New Antiviral Drugs: Incivek, Victrelis and Edurant

1. End-stage liver disease due to HCV infection currently represents the major indication for liver transplantation in the Western world.
   a. True   b. False

2. Most patients who contract HCV will develop chronic:
   a. cirrhosis.   c. lymphoma.
   b. infection.   d. nephrosis.

3. The interferon used in early trials for management of HCV was interferon:
   a. delta.   c. beta.
   b. gamma.   d. alfa.

4. Ribavirin exerts its activity against several:
   a. adenoviruses.   c. flaviviruses.
   b. ectoviruses.   d. retroviruses.

5. The form of interferon that allows for once-weekly rather than thrice-weekly injections is:
   a. acetylated.   c. pegylated.
   b. glycolated.   d. ricinolated.

6. Incivek is indicated for treatment of which form of chronic hepatitis C?
   a. Genotype 1   c. Genotype 3
   b. Genotype 2   d. Genotype 4

7. Incivek is an inhibitor of HCV NS3/4A serine:
   a. amylase.   c. nuclease.
   b. lipase.   d. protease.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] 6. [a] [b] [c] [d] 11. [a] [b] [c] [d]
2. [a] [b] [c] [d] 7. [a] [b] [c] [d] 12. [a] [b]
3. [a] [b] [c] [d] 8. [a] [b] 13. [a] [b] [c]
4. [a] [b] [c] [d] 9. [a] [b] 14. [a] [b] [c] [d]
5. [a] [b] [c] [d] 10. [a] [b] [c] [d] 15. [a] [b] [c] [d]

I am enclosing $10 (member); $15 (nonmember) for this month's quiz made payable to: Ohio Pharmacists Association.

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
   2. Did it meet each of its objectives?  yes  no
   If no, list any unmet
   3. Was the content balanced and without commercial bias?  yes  no
   4. Did the program meet your educational/practice needs?  yes  no
   5. How long did it take you to read this lesson and complete the quiz?
   6. Comments/future topics welcome.

To receive CE credit, your quiz must be postmarked no later than January 15, 2015. A passing grade of 80% must be attained. CE statements of credit are mailed February, April, June, August, October, and December until the CPE Monitor Program is fully operational. Send inquiries to opa@ohiopharmacists.org.