Pharmacotherapy for Hepatitis C Virus Infection

Candice Nickens Frye, PharmD

Objectives
- Describe the epidemiology of hepatitis C virus infection and its relationship to liver disease.
- Review the diagnostic tests available for hepatitis C virus infection.
- Delineate the treatment goals for the management of acute and chronic hepatitis C virus infection.
- Review the current therapeutic options for the treatment and management of hepatitis C virus infection.

Abstract
Hepatitis C virus (HCV) infection is the leading cause of liver failure. Three million persons in the U.S. are infected with the virus, and intravenous drug use is the primary mode of transmission. HCV mortality rates are increasing in certain populations (i.e., in African-American and white men). Although newer therapy has allowed for higher percentages of sustained virological responses, treatment remains complex and extremely uncomfortable.

Introduction
Identified more than a decade ago, hepatitis C virus (HCV) is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) and is the primary indication for liver transplantation in the U.S. This common chronic blood-borne infection affects approximately 3.8 million people in the U.S., with more than 50% of these cases occurring in adults between the ages of 30 and 49. However, the peak prevalence of chronic HCV is in the fourth and fifth decades of life (Figure 1). Although the infection resolves in 15% of patients, it becomes chronic in 85% of those infected. This article reviews the overall impact of HCV infection on society and health care.

Epidemiology and Distribution
The National Health and Nutrition Examination Survey (NHANES) study concluded that 1.5% of Caucasians, 3.2% of African-Americans, and 2.1% of the Hispanic population are infected with HCV. The peak prevalence of anti-HCV, the antibody to HCV, occurs in the fourth and fifth decades of African-Americans but peaks in the fourth decade in Caucasians. In fact, anti-HCV is two to three times more common in African-Americans, with African-American men appearing to have a higher rate of chronicity (90%–95%) than Caucasians and a lower rate of viral clearance after acute infection. The higher prevalence of HCV among African-Americans has been correlated with a lower socioeconomic status, genetic variables, specific genes, and immunological status. In any group, the overall true incidence of infection and the extent of morbidity become difficult to estimate because of the high number of asymptomatic, acute HCV cases and the prolonged natural history of disease.

Cost
Cost is an important variable in the treatment of patients with HCV infection. It becomes a critical variable in providing quality health care, especially in patients with coexisting human immunodeficiency virus (HIV). In 2001, the American Gastroenterological Association (AGA) estimated a total of 317,000 outpatient visits for HCV treatment in the U.S., with the cost of outpatient services projected at $23.9 million and the cost of antiviral therapy averaging $530 million. Leigh et al. discovered total HCV costs, direct and indirect, to be approximately $5.46 billion (nine times that projected by the AGA), with chronic liver disease accounting for 92% and primary liver cancer contributing to 8% of the total costs (excluding pain and suffering). Because mortality rates for patients with HCV are still increasing, costs need to be assessed regularly to cover all patient variables, including therapy, socioeconomic status, lifestyle, employment earnings, fringe benefits, length of hospital stay, pain, suffering, and other disease states as well as the expenditures for homeless, incarcerated, and institutionalized persons.

Virus Biology
First identified in 1988, HCV infection is caused by a small,
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A single-stranded RNA virus that is a member of the genus *Hepacivirus* and the family *Flaviviridae*.9–12 HCV replicates in the cytoplasm of hepatocytes and B lymphocytes.9 Persistent infection or a lack of viral clearance is related to continuous virus production and to the loss of helper T-cells.13,14 Genetic analysis reveals the existence of numerous subtypes, or genotypes. HCV has at least six major genotypes (1–6), which are found in clusters around the world, and 50 subtypes (i.e., 1a, 1b).10,15,16 The ability to identify the viral subtypes is extremely important in determining specific responses to treatment:

- **Genotype 1** is the most common subtype, accounting for 76% of HCV cases in the U.S. Genotypes 1a and 1b account for 45% and 30% of those cases, respectively.17
- **Genotypes 2–6** are located throughout the world. Each has major epidemiological significance and varies greatly in sensitivity to antiviral therapy (Table 1).18,19

 Patients with genotypes 1a and 1b, most commonly observed in African-Americans, do not respond effectively to interferon monotherapy, and only 10% to 15% of treated patients exhibit a long-term response.20 Genotypes 2 and 3 are more responsive to therapy, with patients sometimes receiving a shorter duration of treatment (24 weeks vs. 48 weeks).21

**Viral Transmission**

HCV is contracted primarily via blood or blood products, with intravenous (IV) drug use accounting for at least 68% of new HCV infections.10 Prior to the advent of blood donor screening and surrogate hepatitis testing (using diagnostic viral markers) in 1992, blood transfusions and plasma-derived products were associated with a significant risk of HCV transmission.17 Today, transfusions comprise only 3% of cases. Sexual transmission of HCV accounts for fewer than 10% of all cases, and infection is statistically associated with sexual exposure to high-risk individuals or people with a history of high-risk sexual activity.22–25 Other routes of parenteral transmission are presented in Figure 2.26–30

**Disease Progression**

Acute HCV infection is rarely studied, primarily because (1) the disease is asymptomatic, (2) the incidence is infrequent, (3) diagnostic tests are not commonly used, and (4) it is difficult to differentiate acute from chronic reactivation phases. Of those patients acutely infected with HCV, 81% progress to chronic HCV within six months.

A major concern for patients with chronic HCV is the time of progression to fibrosis, cirrhosis, or hepatocellular carcinoma (HCC).24 From analyses of retrospective and prospective data, almost 15% to 20% of patients with HCV infection progress to cirrhosis, with 5% progressing to HCC.32 Numerous factors that result in advanced stages of liver disease (i.e., fibrosis) include older age, excessive alcohol consumption, or having an advanced state of fibrosis at the time of the initial liver biopsy.33–35 In general, the natural history of HCV differs according to geography, virus characteristics (e.g., genotype, viral load), co-infection with other viruses, and other unexplained factors.

**Diagnosis**

The HCV serological assays that are most commonly used to confirm antibody to HCV (anti-HCV) include the enzyme immunoassay (EIA) and the recombinant immunoblot assay (RIBA). Three generations of EIA antibody testing exist, all having a sensitivity and specificity exceeding 95%.1,36 EIA-2, the most commonly used assay, is recommended as the initial screening test; it is reproducible, inexpensive, and suitable for screening high-risk populations.37 Because of the high level of specificity and sensitivity of the EIA, confirmation with
methods such as the RIBA are becoming unnecessary. Quantitative HCV assays, such as polymerase chain reaction (qPCR) and branched-chain DNA (bDNA), are commonly used in clinical practice and also confirm the diagnosis of HCV by measuring HCV RNA particles in the blood.1

The relevance of using serum amino-transferase (ALT) to determine disease activity has been extensively debated. ALT is the most inexpensive and non-invasive means of detecting disease activity, but it is limited in its ability to assess the degree of disease activity and disease progression. In the past, ALT had been a primary marker of liver disease; however, approximately 30% of patients with chronic hepatitis C have normal ALT levels, and another 40% have ALT levels that are less than two times the upper limit of normal (ULN).38 Patients with normal ALT levels have a decreased risk of disease progression and present with only minimal inflammation and mild or no fibrosis.39,40

Although some may progress to advanced stages of disease even though they have normal ALT levels,39-42 Abnormal ALT levels lasting longer than six months, if confirmed on repeated testing, should prompt a search for risk factors for infection and a battery of serological tests, including those for hepatitis B virus and an EIA for the presence of HCV antibody.32

The use of genotype assays is an excellent way of predicting patients’ responses to therapy, especially in patients with genotypes 1a and 1b.

The liver biopsy, despite its cost and discomfort, is the most widely used diagnostic method of detecting liver disease. Although this high-risk, invasive procedure is not cost-effective, it provides important information (e.g., inflammatory grade and fibrotic stage) to help exclude other liver diseases as well as insight into early disease management and prognosis.43,44

Management

Although great strides have been made in the treatment of chronic HCV infection since the discovery of the virus in 1989, therapy remains problematic. Most patients with chronic infection (defined by the detection of HCV RNA for at least six months)45 have few signs and symptoms of disease. Infrequent signs and symptoms include fatigue, right upper-quadrant pain, nausea, and poor appetite.45,46 Selecting patients for treatment would be simpler if the current therapy (1) were less complicated, (2) carried high rates of sustained responses, (3) were simple to administer, (4) were required for a shorter time period, and (5) were easy to tolerate.

The duration of therapy is normally 24 or 48 weeks,21 and the goals of therapy are assessed by the end-of-treatment response (ETR) or by the sustained virological response (SVR).1,9,32

Patients with undetectable viral loads (fewer than 100 copies/ml) at the cessation of therapy are said to have an ETR. The SVR can be defined as an HCV RNA viral load of 50 copies/ml or fewer, 24 weeks after treatment has stopped.32,45

The primary goal of therapy is to decrease viral loads to undetectable levels and to achieve SVRs that will lead to histological improvement and a reduced risk of viral transmission.37 When patients do achieve SVRs, viral loads tend to remain undetectable for years.

Five distinct characteristics have been associated with SVRs:48

- genotype 2 or 3
- viral loads below 3.5 million copies/ml at the baseline evaluation
- minimal or no portal fibrosis
- female sex
- age younger than 40

According to the National Institutes of Health consensus guidelines for the management of HCV infection, all patients with chronic HCV (detectable HCV RNA viral loads of 50 IU/ml or greater) and those at an increased risk for cirrhosis should be treated. Because therapy for chronic HCV infection is far from ideal, practitioners must consider many factors before making a final therapeutic decision for a given patient. In addition to receiving antiviral therapy for HCV, all patients should receive hepatitis A and B vaccine to decrease the incidence of morbidity and mortality.49

Interferons (IFNs), which are glycopeptides derived from white blood cells in response to infection, have been the mainstay of HCV therapy since 1991;50 however, they yield poor virological response rates.51,52 At the beginning of the HCV
epidemic, the initial treatment was IFN alfa-2b monotherapy, consisting of 3 million units (MU) three times weekly for 48 weeks or longer, depending on SVR rates at three months. However, because IFN alfa-2b did not show increased efficacy in induction trials, it is now reserved only for patients who cannot tolerate combination therapy with IFN alfa-2b and ribavirin, a nucleoside analogue with antiviral activity against several DNA and RNA viruses.

For patients who have received IFN monotherapy and have experienced a relapse (the re-emergence of HCV RNA after previous undetectable levels at the end of treatment), an increased dose of IFN or a combination product of IFN alfa-2b and ribavirin (Rebetol®, Schering-Plough) has been found to be effective. Ribavirin is well absorbed and is administered according to the patient’s weight; however, it has little to no activity against HCV when used as monotherapy. With this two-drug regimen, approximately 40% of patients achieve SVRs and the associated long-term benefits.55

Two large, randomized, controlled clinical trials compared combination therapy with IFN alfa-2b monotherapy. Patients receiving the combination therapy had SVRs at 24 weeks (33%) and at 48 weeks (41%); patients receiving monotherapy had lower rates of SVRs at 24 weeks (6%) and at 48 weeks (16%). Genotype 1 patients, who received treatment for a longer period, had lower response rates than patients with genotypes 2 and 3.

Another interferon, IFN alfa-2a, also yielded low SVR rates in clinical trials. IFN alfa-2a differs from IFN alfa-2b in its peptide sequence by only one amino acid and demonstrates a safety and efficacy profile similar to that of other alpha interferons.

IFN alfacon-1 (Infergen®, Amergen) plus Consensus IFN (high-dose Infergen®, or CIFN) is a genetically engineered compound that shares 88% homology with IFN alfa and 30% with IFN beta. This agent has greater cytokine induction and antiviral activity than both IFN alfa-2a and 2b, but it is not commonly used because viral response rates have been similar to those achieved with standard IFN alfa monotherapy.

Dosing and Formulations

The current gold standard for treatment of HCV is pegylated IFN alfa-2b combined with ribavirin for 48 weeks, depending on the genotype. However, more than 50% of patients do not respond completely to combination therapy, suggesting the need for more treatment options, such as ribavirin. The manufacturer recommends that patients weighing 75 kg or less receive 1,000 mg/day of ribavirin and that patients weighing 75 kg or more receive 1,200 mg/day.

There are two formulations of pegylated interferon, with each differing in their pharmacokinetic and chemical properties.

Peginterferon alfa-2b (Peg-Intron®, Schering-Plough) has a smaller molecule of peg (12 kD) attached to the protein than the newly approved peginterferon alfa-2a (Pegasys®, Roche), which has a larger peg molecule (40 kD) attached to IFN. Pegylated IFN alfa-2b, which was approved by the Food and Drug Administration (FDA) in October 2001, is a modified form of IFN alfa-2b.

Pegylated IFN alfa-2b has an added polyethylene glycol molecule, which produces a biologically active molecule with more favorable pharmacokinetics. Peginterferon alfa-2a, which was approved by the FDA in 2002, has sustained absorption and an extended half-life equal to that of peginterferon alfa-2b.

One of the most valuable properties of pegylated interferons is their decreased systemic clearance rate plus a prolonged plasma half-life, allowing for once-weekly administration. As a result of this reduced clearance rate, these interferons have more exposure and enhanced efficacy than do nonpegylated proteins; they can stay in the body and fight off the virus for a longer time compared with other interferon agents.

Clinical trials have shown that although pegylated IFN alfa-2b monotherapy improves SVR rates (30% vs. 5%–10%) for genotype 1, compared with conventional IFNs, relapse rates after cessation of therapy are still high. Manns et al. found that HCV-infected patients who took pegylated IFN alfa-2b (3 million units SQ) plus oral ribavirin (1,000–1,200 mg/day) for 48 weeks had higher SVR rates than patients taking low-dose pegylated IFN alfa-2b plus ribavirin or IFN alfa-2b (3 million units SQ) plus ribavirin (1,000–1,200 mg/day orally) for 48 weeks (54% vs. 47% vs. 47%). In addition, patients with genotype 1 had SVR rates of 42% vs. 34% vs. 33%, respectively.

Fried et al. compared the use of peginterferon alfa-2a plus ribavirin or placebo with that of IFN alfa-2b plus ribavirin in 1,211 patients. Significantly more patients taking peginterferon alfa-2a plus ribavirin had higher ETRs than did patients taking IFN alfa-2a plus ribavirin (69% vs. 52%, P < .001) or peginterferon alfa-2a plus placebo (69% vs. 59%, P < .01). The SVR rates of patients receiving peginterferon alfa-2a plus ribavirin were significantly greater than those of patients taking IFN alfa-2a plus ribavirin (56% vs. 44%, P < .001) or peginterferon alfa-2a plus placebo (56% vs. 29%, P < .001).

In assessments of responses to various therapies based on genotype, patients with genotype 1 who received peginterferon alfa-2a plus ribavirin had higher SVR rates (48%) than did patients who received IFN alfa-2b plus ribavirin (36%). Patients with HCV genotype 2 or 3 and who received peginterferon alfa-2a plus ribavirin had higher SVR rates than patients taking IFN alfa-2b plus ribavirin (76% vs. 61%, P = .005) (Table 2).

In general, the new pegylated formulations appear to offer enhanced SVR rates in all groups, regardless of genotype or viral load, and the once-weekly dosing makes this form preferable to other interferon therapies.

Adherence to medication regimens is always a major concern in disease treatment. The primary cause of patient nonadherence is the intolerable adverse drug effects (ADEs) of anti-HCV therapy, which are, at times, difficult to tolerate and control.

IFNs can cause flu-like symptoms during the first month of therapy, bone marrow suppression, and psychiatric illness. These symptoms often appear 12 hours after the dose is taken and disappear 24 hours after dosing, despite elevated serum IFN concentrations.

Neutropenia and thrombocytopenia are manageable when the IFN dosage is reduced and when IFN therapy is discontinued, but blood counts usually return to those of the baseline examination after four weeks of therapy.
Psychiatric illnesses (e.g., depression, irritability, suicidal ideations) and insomnia are sometimes associated with IFN therapy and occur at even higher rates when IFNs are administered with ribavirin. From the onset, patients with a history of depressive illness or psychosis should probably not be considered candidates for any IFN formulations. Other ADEs include thyroid dysfunction, rash, headache, and reversible arthralgias.69

Adverse Drug Reactions

A predose of acetaminophen (500 mg–1 g) is commonly administered at bedtime to patients who are taking IFNs to reduce the incidence of flu-like symptoms (e.g., myalgia in 56% of patients and arthralgia in 34%). Other ADEs include alopecia (36%), nausea (43%), anorexia (32%), weight loss (29%), and pruritus (29%). Patients with untreated autoimmune thyroid disease, neutropenia, thrombocytopenia, organ transplantation (other than liver), symptomatic heart disease, decompensated cirrhosis, uncontrolled seizures, or active alcohol or IV drug usage should probably not receive any formulations of IFN. Men and women should be advised to use two methods of contraception and should not plan to conceive during any course of IFN therapy and for up to six months after the discontinuation of treatment.

Ribavirin may cause mild anemia (a hemoglobin count of 8–10 g/dl) or severe anemia (below 8 g/dl); this is a common occurrence in nearly all patients and is a result of dose-dependent hemolysis of red blood cells with ribavirin doses of 1,200 to 1,600 mg/day. The anemia is manageable upon a dose reduction of 800 mg/day or upon discontinuation of ribavirin.62 Other ADEs include fatigue, depression, rash, cough, shortness of breath, and irritability.65 Men and women should be advised to use two methods of contraception and should not plan to conceive during any course of ribavirin therapy and for up to six months after the discontinuation of treatment.

Monitoring

It is essential to monitor patients during anti-HCV therapy and to keep track of all regimens, including herbal therapies. Patients need to be responsible and to return for regular follow-up examinations, and practitioners should maintain accurate and detailed records for all patients. During patient evaluations, physicians should schedule regular evaluations such as psychological assessments, urinalyses, pregnancy tests, serum chemistry profiles, blood counts, and thyroid hormone levels.

Hepatitis C Virus/Human Immunodeficiency Virus Co-infection

The coexistence of HCV and HIV poses a larger problem for the management of HCV. Because the modes of HIV and HCV transmission are similar, approximately 15% to 30% of HIV patients also become infected with HCV. Patients who have not used protease inhibitors (PIs) and those who consume

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**Table 2: Treatment of Hepatitis C Virus Infection**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name and Manufacturer</th>
<th>Dose</th>
<th>Duration of Therapy*</th>
<th>HCV Genotype-1 Only (Average Percentage of Sustained Virological Response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2b</td>
<td>Intron® A (Schering)</td>
<td>3 million units SQ three times weekly</td>
<td>48 wk</td>
<td>13%–20%</td>
</tr>
<tr>
<td>Interferon alfa-2a</td>
<td>Roferon® (Roche)</td>
<td>3–5 million units SQ three times weekly</td>
<td>48 wk</td>
<td>25%</td>
</tr>
<tr>
<td>Interferon alfacon-1</td>
<td>Infergen® (Amgen)</td>
<td>9 mcg SQ three times weekly</td>
<td>48 wk</td>
<td>13%–20%</td>
</tr>
<tr>
<td>or Consensus interferon</td>
<td>High-dose Infergen®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-2b</td>
<td>Rebetron® (Schering-Plough)</td>
<td>3 million units SQ three times weekly</td>
<td>48 wk</td>
<td>28%–31%</td>
</tr>
<tr>
<td>+ Ribavirin</td>
<td></td>
<td>800–1,200 mg orally daily (based on weight)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2b</td>
<td>PegIntron® (Schering-Plough)</td>
<td>1–1.5 mcg/kg SQ weekly</td>
<td>48 wk</td>
<td>42%</td>
</tr>
<tr>
<td>+ Ribavirin</td>
<td>Rebetol® (Schering-Plough)</td>
<td>800–1,200 mg/day orally (based on weight)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td>Pegasys® (Roche)</td>
<td>180 mcg/wk</td>
<td>48 wk</td>
<td>46%</td>
</tr>
<tr>
<td>+ Ribavirin</td>
<td>Rebetol® (Schering-Plough)</td>
<td>1,000–1,200 mg/wk (based on weight)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SQ = subcutaneously; wk = week. Data from References 52–54, 57, 60, 64, and 65.
excessive alcohol or who have low CD4 T-cell counts progress more rapidly to cirrhosis than patients without HCV. For patients with both HCV and HIV infections, concerns arise about drug–drug interactions between therapies used for each disease and drug–disease interactions, such as the increased incidence of hepatotoxicity from antiretroviral therapy combined with underlying hepatic dysfunction resulting from HCV.

The effect of HCV co-infection on the natural history of HIV is controversial. Studies have shown that HCV seropositivity can increase the progression to a new AIDS-defining illness or death. Other studies have concluded that in assessing the effect of HCV co-infection on clinical and immunological progression of HIV-1 disease and the response to highly active antiretroviral therapy (HAART), HCV-infected patients are the least likely to receive HAART. In addition, no differences were found in the risk of an AIDS-defining illness among HCV-infected patients, compared with patients not infected with HCV, even when various CD4 cell count ranges were compared between the groups.

Selecting the appropriate regimen for treating HIV alone is a challenge in and of itself, but pharmacotherapeutic management is even more challenging when HIV infection is coupled with HCV infection. Drug–drug interactions that occur with HCV/HIV therapies can cause an increased incidence of hepatotoxicity from antiretroviral therapy combined with underlying hepatic dysfunction resulting from HCV.

The natural history of the illness is slowly progressive (the median time to cirrhosis is 28 to 32 years). HCV-positive patients should not donate blood, organs, tissues, or semen. Because the risk of sexual transmission is small, barrier protection (e.g., condoms) is not recommended; however, barrier methods can decrease the risk of transmission of HCV and other sexually transmitted diseases as well.

Although transmission of the virus from mother to child is rare, transmission rates are higher in HIV-positive mothers.

Breast-feeding is not contraindicated for HCV-positive patients.

Household members should avoid third-party contact with blood by not sharing toothbrushes, razors, and needles, and they should cover open wounds.

The use of standard precautions to prevent transmission to health care providers and patients is essential in all health care facilities.

Needle-and-syringe exchange programs may help reduce parenterally transmitted HCV infection as well as other infections, such as HIV.

Scheduled classes on medication use and adverse effects and their management can help enhance patients’ understanding of HCV infection.

HIV = human immunodeficiency virus.

### Drugs in Development

Future therapies for the management of HCV infection are under development, and at least 15 agents are in the pipeline. Antiviral agents that directly attack enzymes used by the virus to replicate itself are needed to slow disease progression. Researchers are currently studying the use of protease, helicase, and polymerase inhibitors, but limited data have been reported. DNA vaccines, which would stimulate T-cell activity, and antisense agents, which would work by binding to interferon-resistance sites, are also potential tools for preventing and managing the illness. Therapy within the next five years will probably take the form of multidrug combinations and will, ideally, offer a more tolerable side-effect profile, achieve a better compliance rate among patients, and reduce serum HCV RNA levels.

Educating patients about adherence to medication is an important factor in controlling HCV infection and should be emphasized at every patient visit when therapy is initiated (Table 3). With HIV treatment, antiretroviral medication adherence at a rate below 95% can prevent complete virological suppression; the same holds true for anti-HCV therapy. Adherence at week 12 is associated with a high probability of achieving SVRs. HCV infection can be controlled with early detection, proper therapy, and patient education.

### Conclusion

Chronic HCV infection is a major public health concern, affecting primarily African-American men in the fourth and fifth decades of life. A significant degree of morbidity and mortality is associated with HCV.

Because the virus can lie dormant for decades before signs or symptoms occur, practitioners are faced with the challenge of trying to prevent and control its spread. Because this is a blood-borne disease, health care workers and high-risk groups such as IV drug users and HIV-positive patients, should be informed about the risks and should undergo testing. Using the EIA to detect HCV and following up with PCR is the current standard for the initial diagnosis.

Newer agents are being developed, but until they are approved, we do not have enough effective treatment options, especially for patients with genotype 1b.

### References

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**Disclosure**

Dr. Nickens Frye has indicated that she has no commercial relationships to disclose. This article contains information on unapproved uses.